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(54) Derivatives of 4-oxo-1,4-dihydronicotinic acid

(57) This invention relates to novel 4-oxo-1,4-dihydronicotinic acid derivatives and their salts which have a broad antibacterial spectrum and a low toxicity, and are useful for treatment of diseases of human beings and animals, to a process for producing the same and to an antibacterial agent containing the same.

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The Chemical formula(e) appearing in the printed specification was/were submitted after the date of filing, the formula(e) originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

Novel 4-oxo-1,4-dihydronicotinic acid derivatives and salts thereof, process for producing the same, and antibacterial agents containing the same

This invention relates to a novel 4-oxo-1,4-dihydronicotinic acid derivative and its salt, a process for producing the same, and an antibacterial agent containing the same.

The inventors of this invention have cnnducted extensive research to find a compound having a broad antibacterial spectrum, namely an excellent antibacterial activity against Gram-positive and Gram-negative bacteria, having a low toxicity, giving a high blood level when administered orally or parenterally and exhibiting a high effect on the treatment of diseases of human beings and animals. As a result, it has been found that a 4-oxo-1,4-dihydronicotinic acid derivative or its salt different in chemical structure from various commercially available antibacterial agents have the above-mentioned properties.

An object of this invention is to provide a novel antibacterial compound having a broad antibacterial spectrum and a process for producing the same.

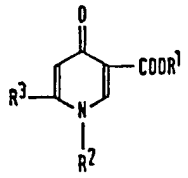
Another object of this invention is to provide an antibacterial compund having a low toxicity.

A further object of this invention is to provide an antibacterial compound which can be well absorbed orally or parenterally.

A still further object of this invention is to provide an antibacterial compound having an excellent effect on the treatment of diseases of human beings and animals.

Other objects and advantages of this invention will become apparent from the following description.

According to this invention, there is provided a 4-oxo-1,4-dihydronicotinic acid derivative and its salt, said derivative being represented by the formula (I),



(I)

wherein R^1 represents a hydrogen atom or a carboxyl-protecting group; R^2 represents a substituted aryl group or a substituted or unsubstituted heterocyclic group; and R^3 represents a haloalkyl group, an aminoalkyl group or a substituted or unsubstituted alkenyl, aralkenyl, aralkyl, aralkadienyl, aralkynyl, heterocyclic alkyl, heterocyclic alkenyl, aryl, cycloalkyl, cycloalkenyl, acyl, iminoalkyl, heterocyclic or bridged hydrocarbon group, a process for producing the same, and an antibacterial agent containing the same.

In the formulas described herein, R^1 is a hydrogen atom or a carboxyl-protecting group. The carboxyl-protecting groups are available and include ester-forming groups which can be removed by catalytic reduction, chemical reduction or other treatments under mild conditions; ester-forming groups which can easily be removed in living bodies; and other known ester-forming groups which can easily be removed by treatment with water or an alcohol. such as organic silyl-containing groups, organic phosphorus-containing groups, organic tin-containing groups, or the like.

Examples of typical carboxyl-protecting groups are:

(a) Alkyl groups, for example C_{1-4} alkyl;

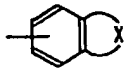
(b) Substituted lower alkyl groups, at least one of the substituents of which is halogen, nitro, acyl, alkoxy, oxo, cyano, hydroxy, di-C_{1-4} alkylamino, cycloalkyl, aryl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, 5-alkyl-2-oxo-1,3-dioxol-4-yl, 1-indanyl, 2-indanyl, furyl, pyridyl, 4-imidazolyl, phthalimido, succinimido, azetidino, aziridino, pyrrolidino, piperidino, morpholino, thiomorpholino, pyrrolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, thi triazolyl, oxatriazolyl, triazolyl, tetrazolyl, quinolyl, phenazinyl, benzofuryl, benzothienyl, benzoxazolyl, benzothiazolyl, coumarinyl, N-lower alkylpiperazino, 2,5-dimethylpyrrolidino, 1,4,5,6-tetrahydropyrimidinyl, 4-methylpiperidino, 2,6-dimethylpiperidino, 4-(5-methyl-2-pyrrolinyl), 4-(2-pyrrolinyl), N-methylpiperidinyl, 1,3-benzodioxolanyl, alkylamino, dialkylamino, acyloxy, acylamino, acylthio, dialkylaminocarbonyl, alkoxycarbonylamino, alkenyloxy, aryloxy, aralkyloxy, alicycle-oxy, heterocycle-oxy, alkoxycarbonyloxy, alkenyloxycarbonyloxy, aryloxycarbonyloxy, aralkyloxycarbonyloxy, alicycleoxycarbonyloxy, heterocycle-oxycarbonyloxy, alkenyloxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, alicycleoxycarbonyl, heterocycle-oxycarbonyl, alkylanilino or alkylanilino substituted by halogen, lower alkyl, or lower alkoxy;

(c) Cycloalkyl groups, lower-alkyl-substituted cycloalkyl groups, or [2,2-di(lower alkyl)-1,3-dioxolan-4-yl]methyl groups;

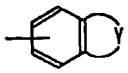
(d) Alkenyl groups;

(e) Alkynyl groups;

(f) Phenyl group, substituted phenyl groups, at least one of the substitutents of which is selected from the substituents exemplified in above (b); or aryl groups represented by the formula:



wherein $-X-$ is $-CH=CH-O-$, $-CH=CH-S-$, $-CH_2CH_2S-$, $-CH=N-CH=N-$, $-CH=CH-CH=CH-$, $-CO-CH=CH-CO-$, or $-CO-CO-CH=CH-$, or substituted derivatives thereof, the substituents of which are selected from those exemplified in above (b), or the formula:



wherein $-Y-$ is a lower alkylene group such as $-(CH_2)_3-$ and $-(CH_2)_4-$, or substituted derivatives thereof, the substituents of which are selected from those exemplified in above (b);

(g) Aralkyl groups which may be substituted, at least one of the substituents of which is selected from those exemplified in above (b);

(h) Heterocyclic groups which may be substituted, at least one of the substituents of which is selected from those exemplified in above (b);

(i) Alicyclic indanyl or phthalidyl groups or substituted derivatives thereof, the substituent of which is halogen or methyl; alicyclic tetrahydronaphthyl groups, or substituted derivatives thereof, the substituent of which is halogen or methyl; trityl group, cholesteryl group, or bicyclo[4,4,0]-decyl group;

(j) Alicyclic phthalidylidene-lower alkyl group or substituted derivatives thereof, the substituent of which is halogen or lower alkyl group.

The carboxyl-protecting groups listed above are typical examples, and there may be used any groups selected from those disclosed in U.S. Patents 3,499,909; 3,573,296; and 3,641,018, West German Offenlegungsschrift 2,301,014; 2,253,287; and 2,337,105.

Among them, preferable carboxyl-protecting groups are those which can radily be removed in living bodies such as 5-lower alkyl-2-oxo-1,3-dioxol-4-yl-lower alkyl groups, acyloxyalkyl groups, acylthioalkyl groups, phthalidyl group, indanyl group, phenyl group, substituted or unsubstituted phthalidylidene-lower alkyl groups or groups represented by the formulas:

$$-\underset{\displaystyle R^5}{\underset{|}{CH}}(CH_2)_mOR^4, \quad -\underset{\displaystyle R^5}{\underset{|}{CH}}OCOOR^6 \quad \text{and} \quad -\underset{\displaystyle R^7}{\underset{|}{CH}}(CH_2)_mCOOR^4$$

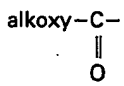
wherein R^4 represents a hydrogen atom or a straight or branched chain substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, alicyclic, or heterocyclic group; R^5 represents a hydrogen atom or an alkyl group; R^6 represents a straight or branched chain substituted or unsubstituted alkyl, alkenyl, aryl, aralyl, alicyclic, or heterocyclic group; R^7 represents a hydrogen atom, a halogen atom or a substituted or unsubstituted alkyl, cycloalkyl, aryl or heterocyclic group or $-(CH_2)_n-COOR^4$ wherein R^4 is as defined above and n represents 0, 1 or 2, and m represents 0, 1 or 2.

The above-mentioned preferable carboxyl-protecting groups include specifically 5-lower alkyl-2-oxo-1,3-dioxol-4-yl-lower alkyl groups such as 5-methyl-2-oxo-1,3-dioxol-4-ylmethyl, 5-ethyl-2-oxo-1,3-dioxol-4-ylmethyl, 5-propyl-2-oxo-1,3-dioxol-4-ylmethyl, and the like; acyloxyalkyl groups, such as acetoxymethyl, pivaloyloxymethyl, propionyloxymethyl, butyryloxymethyl, isobutyryloxymethyl, valeryloxymethyl, 1-acetoxy-ethyl, 1-acetoxy-n-propyl, 1-pivaloyloxy-ethyl, 1-pivaloyloxy-n-propyl and the like; acylthioalkyl groups such as acetylthiomethyl, pivaloylthiomethyl, benzoylthiomethyl, p-chlorobenzoylthiomethyl, 1-acetylthio-ethyl, 1-pivaloylthio-ethyl, 1-benzoylthioethyl, 1-(p-chlorobenzoylthio)-ethyl and the like; alkoxymethyl groups such as methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, butyloxymethyl and the like; alkoxycarbonyloxy-lower alkyl groups such as methoxycarbonyloxymethyl, ethoxycarbonyloxymethyl, propoxycarbonyloxymethyl, isopropoxycarbonyloxymethyl, n-butyloxycarbonyloxymethyl, tert.-butyloxycarbonyloxymethyl, 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl, 1-propoxycarbonyloxyethyl, 1-isopropoxycarbonyloxyethyl, 1-butyloxycarbonyloxyethyl and the like; alkoxycarbonylalkyl groups such as methoxycarbonylmethyl, ethoxycarbonylmethyl and the like; phthalidyl group; indanyl group; phenyl group; and phthalidylidenealkyl groups such as 2-(phthalidylidene)-ethyl, 2-(5-fluorophthalidylidene)-ethyl, 2-(6-chlorophthalidylidene)-ethyl, 2-(6-methoxyphthalidylidene)-ethyl and the like.

In respect of R^2 and R^3 in the formula [I], the aryl group includes, for example, phenyl, naphthyl and the like, and the heterocyclic group includes 5-membered, 6-membered and fused ring type heterocyclic groups having at least one atom selected from N, S and O such as, thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxaxolyl, isoxazolyl, furazanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl,

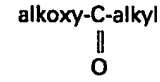
pyrazolidinyl, pyrazolinyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, thiatriazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, piperidinyl, piperazinyl, pyranyl, morpholinyl, pyridine-1-oxide-3- or 4-yl, pyridazine-1-oxide-6-yl, quinoline-1-oxide-6-yl, triazinyl, benzothienyl, naphthothienyl, benzofuryl, 2,3-dihydrobenzofuryl, benzothiazolyl, isobenzofuryl, chromenyl, indolidinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolyl, 1,2,3,4-tetrahydroquinolyl, 1,2-dihydroquinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, 1,2,3,4-tetrahydroquinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, isochromanyl, chromanyl, indolinyl, isoindolinyl, benzoxazolyl, benzomorpholinyl, triazolopyridyl, tetrazolopyridazinyl, tetrazolopyrimidinyl, thiazolopyridazinyl, thiadiazolopyridazinyl, triazolopyridazinyl and the like. Furthermore, the haloalkyl group in R^3 includes halo-C_{1-8}alkyl groups, for example, fluoromethyl, chloromethyl, bromomethyl, 1- or 2-fluoroethyl, 1- or 2-bromoethyl, 1- or 2-chloroethyl and the like. The aminoalkyl group in R^3 includes amino-C_{1-8}alkyl groups, for example, aminomethyl, 1-aminoethyl, 2-aminoethyl, and the like. The alkenyl group in R^3 includes C_{2-8}alkenyl groups, for example, vinyl, allyl, isopropenyl, 1-propenyl, 2-butenyl, 2-pentenyl and the like. The aralkenyl group in R^3 includes the above-mentioned alkenyl groups which have been substituted by the above-mentioned aryl group. The aralkyl group in R^3 includes C_{1-8}alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, hexyl, octyl and the like which have been substituted by the above-mentioned aryl group. The aralkadienyl group in R^3 includes C_{4-8}alkadienyl groups such as 1,3-butadienyl, 2,4-pentadienyl and the like which have been substituted by the above-mentioned aryl group. The aralkynyl group in R^3 includes C_{2-8}alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl and the like which have been substituted by the above-mentioned aryl group. The heterocyclic alkenyl group in R^3 includes the above-mentioned C_{2-8}alkenyl groups which have been substituted by the above-mentioned heterocyclic group. The heterocyclic alkyl group in R^3 includes the above-mentioned alkyl groups which have been substituted by the above-mentioned heterocyclic group. The cycloalkyl group in R^3 includes C_{3-8}cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. The cycloalkenyl group in R^3 includes C_{3-8}cycloalkenyl groups such as 1-cyclopropenyl, 2-cyclopropenyl, 1-cyclobutenyl, 2-cyclobutenyl, 1-cyclopentenyl, 3-cyclopentenyl, 4-cyclopentenyl, 1-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, cycloheptenyl, cyclooctenyl and the like. The iminoalkyl group in R^3 includes imino-C_{1-8}alkyl groups, for example, iminomethyl, 1-iminoethyl, 2-iminoethyl and the like. The acyl group in R^3 includes formyl group; alkanoyl groups such as acetyl, propionyl and the like; aroyl groups such as benzoyl, p-nitrobenzoyl and the like; and heterocyclic carbonyl group such as thenoyl, furoyl and the like. The bridged hydrocarbon group in R^3 includes C_{4-15} bridged hydrocarbons, such as 3,6-methanocyclohexen-4-yl, adamantyl and the like.

As the substituents for said R^2 and R^3 groups, there may be used halogen atoms, for example, fluorine, chlorine, bromine, iodine and the like; alkyl groups such as straight or branched chain C_{1-10}alkyl groups, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, hexyl, heptyl, octyl and the like; aralkyl groups such as phenyl-C_{1-4}alkyl groups and naphthyl-C_{1-4}alkyl groups, for example, benzyl, phenethyl, naphthylmethyl, naphthylethyl and the like; hydroxyl group; alkoxy groups such as C_{1-10}alkoxy groups, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy , isobutoxy, sec.-butoxy, tert-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy and the like; alkylthio groups such as C_{1-10}alkylthio groups, for example, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec.-butylthio, tert.-butylthio, pentylthio, hexylthio, heptylthio, octylthio and the like; nitro group; cyano group; amino group; alkylamino groups such as C_{1-8}alkylamino groups, for example, methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, sec.-butylamino, tert.-butylamino, and the like; di-alkylamino groups such as di-C_{1-8}alkylamino groups, for example, dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino and the like; alkenylamino groups such as C_{2-8}alkenylamino groups, for example, vinylamino, alkylamino and the like; carboxyl group; carbamoyl group; acyl groups such as formyl group, alkanoyl group, for example, acetyl, propionyl and the like, aroyl groups, for example, benzoyl, p-nitrobenzoyl and the like, and heterocyclic carbonyl groups, for example, thenoyl, furoyl and the like; acyloxy groups, for example acyl-O- groups in which the acyl is the same as mentioned above; acylalkyl groups, for example, the above-mentioned alkyl groups which have been substituted by the above-mentioned acyl group; acylamino groups, for example, acyl-NH- groups in which the acyl is the same as mentioned above; alkoxycarbonyl groups, for example,



groups in which the alkoxy is the same as mentioned above; aminoalkyl groups, for example, NH_2-alkyl groups in which the alkyl is the same as mentioned above; alkylaminoalkyl groups, for example, the above-mentioned alkyl groups which have been substituted by the above-mentioned alkylamino group; dialkylaminoalkyl groups, for example, the above-mentioned alkyl groups which have been substituted by the above-mentioned dialkylamino group; hydroxyalkyl groups, for example, HO-alkyl groups in which the alkyl is the same as mentioned above; hydroxyiminoalkyl groups, for example, HON=alkyl in which the alkyl is the same as mentioned above; alkoxyalkyl groups, for example, the above-mentioned alkyl groups

substituted by the above-mentioned alkoxy group; carboxyalkyl groups, for example, HOOC-alkyl groups in which the alkyl is the same as mentioned above; alkoxycarbonylalkyl groups, for example,



groups in which the alkoxy and the alkyl are the same as mentioned above; sulfoalkyl groups, for example, the above-mentioned alkyl groups substituted by a sulfo group; sulfo group; sulfoxy group; sulfamoyl group; sulfamoylalkyl groups, for example, the above-mentioned alkyl groups which have been substituted by a sulfamoyl group; carbamoylalkyl groups, for example, the above-mentioned alkyl groups which have been substituted by a carbamoyl group; aryl groups, for example, phenyl, naphthyl and the like; arylthio groups, for example, aryl-S- groups in which the aryl is the same as mentioned above; aryloxy groups, for example, aryl-O- groups in which the aryl is the above-mentioned; oxo group; thioxo group; mercapto group; ureido group; hydroxyamino group; hydroxyalkylamino groups, for example, HO-alkyl-NH- groups in which the alkyl is the same as mentioned above; halogenoalkyl groups, such as mono-, di- or tri-halogeno-C_{1-4}alkyl groups; for example, chloromethyl, bromomethyl, dichloromethyl, dibromomethyl, trifluoromethyl, dichloroethyl and the like; C_{2-8}alkenyl groups, for example, vinyl, allyl, isopropenyl, 1-propenyl, 2-butenyl, 2-pentenyl and the like; C_{2-8}alkynyl groups, for example, ethynyl, 1-propynyl, 2-propynyl and the like; alkenylamino groups, for example, alkenyl-NH- groups in which the alkenyl is the same as mentioned above; C_{3-8}cycloalkyl groups, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like; C_{6-8}cycloalkadienyl groups, for example, cyclohexadienyl, cycloheptadienyl and the like; C_{1-4}alkylenedioxy groups, for example, methylenedioxy, ethylenedioxy, trimethylenedioxy and the like; epoxy group; heterocyclic groups, such as 5-membered, 6-membered and fused ring type heterocyclic groups containing at least one atom selected from N, S and O, for example, thienyl, furyl, pyrrolyl, imidazolyl, pyrazoyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, furazanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, thiatriazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, piperidinyl, piperazinyl, pyranyl, morpholinyl, pyridine-1-oxide-2-yl, pyridazine-1-oxide-6-yl, quinoline-1-oxide-6-yl, triazinyl, benzothienyl, naphthothienyl, benzofuryl, 2,3-dihydrobenzofuryl, benzothiazolyl, isobenzofuryl, chromenyl, indolidinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolyl, isoquinolyl, 1,2,3,4-tetrahydroquinolyl, 1,2-dihydroquinolyl, phthalazinyl, naphthylidinyl, quinoxalinyl, 1,2,3,4-tetrahydroquinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, isochromanyl, chromanyl, indolinyl, isoindolinyl, benzoxazolyl, benzomorpholinyl, triazolopyridyl, tetrazolopyridazinyl, tetrazolopyrimidinyl, thiazolopyridazinyl, thiadiazolopyridazinyl, triazolopyridazinyl and the like; and 5-nitrofurfurylideneamino groups and the like. R^2 and R^3 may have at least one of the above-mentioned substituents. In particular, halogen atoms, alkyl groups, hydroxyl group, amino group, alkoxy groups, alkylamino groups, dialkylamino groups, nitro group, aryl groups and heterocyclic groups are preferred as the substituents.

The above-mentioned substituents for R^2 and R^3 may have at least one substituent selected from halogen atoms, hydroxyl group, carboxyl group, nitro group, alkyl groups, alkoxy groups, amino group, alkylamino groups, dialkylamino groups, aryl groups, acyl groups and the like, in which as the halogen atoms, alkyl groups, alkoxy groups, alkylamino groups, dialkylamino groups, aryl groups and acyl groups, there may be used those mentioned above as substituents for R^2 and R^3.

Furthermore, when R^2 and R^3 of the present compound have hydroxyl, amino or carboxyl, these groups may be protected by known protecting groups. As the protecting group for the hydroxyl group, there may be used all groups which can conventionally be used for the protection of hydroxyl group, specifically including readily removable acyl groups such as benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 4-(phenylazo)benzyloxycarbonyl, 4-(4-methoxyphenylazo)benzyloxycarbonyl, tert.-butoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, diphenylmethoxycarbonyl, 2,2,3-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, 2-furfuryloxycarbonyl, 1-adamantyloxycarbonyl, 1-cyclopropylethoxycarbonyl, 8-quinolyloxycarbonyl, formyl, acetyl, chloroacetyl, trifluoroacetyl and the like, as well as benzyl, benzhydryl, trityl, methoxymethyl, tetrahydrofuryl, tetrahydropyranyl, 2-nitrophenylthio, 2,4-dinitrophenylthio and the like. As the protecting group for the amino group, there may be used all groups which can conventionally be used for the protection of amino group, specifically including readily removable acyl groups such as 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, benzyloxycarbonyl, p-toluenesulfonyl, p-nitrobenzyloxycarbonyl, o-bromobenzyloxycarbonyl, o-nitrophenylsulfenyl, acetyl, (mono-, di- or tri-)chloroacetyl, trifluoroacetyl, formyl, tert.-amyloxycarbonyl, tert.-butoxycarbonyl, p-methoxybenzyloxycarbonyl, 3,4-dimethoxybenxyloxycarbonyl, 4-(phenylazo)benzyloxycarbonyl, 4-(4-methoxyphenylazo)benzyloxycarbonyl, pyridine-1-oxide-2-yl-methoxycarbonyl, 2-furyloxycarbonyl, diphenylmethoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, 1-cyclopropylethoxycarbonyl, phthaloyl, succinyl, 1-adamantyloxycarbonyl, 8-quinolyloxycarbonyl and the like, as well as such readly removable groups as trityl, 2-nitrophenylthio, 2,4-dinitrophenylthio, 2-

hydroxybenzylidene, 2-hydroxy-5-chlorobenzylidene, 2-hydroxy-1-naphthylmethylene, 3-hydroxy-4-pyridylmethylene, 1-methoxycarbonyl-2-propylidene, 1-ethoxycarbonyl-2-propylidene, 3-ethoxycarbonyl-2-butylidene, 1-acetyl-2-propylidene, 1-benzoyl-2-propylidene, 1-[N-(2-methoxyphenyl)carbamoyl]-2-propylidene, 1-[N-(4-methoxyphenyl)carbamoyl]-2-propylidene, 2-ethoxycarbonylcyclohexylidene, 2-ethoxycarbonylcyclopentylidene, 2-acetylcyclohexylidene, 3,3-dimethyl-5-oxocyclohexylidene, 4-nitrofurfurylidene and the like, and other protecting groups for amino group such as di- or tri-alkylsilyl and the like. As the protecting groups for carboxyl group, there may be used all groups which can conventionally be used for the protection of carboxyl group, specifically including such groups as methyl, ethyl, n-propyl, iso-propyl, tert.-butyl, n-butyl, benzyl, diphenylmethyl, trityl, p-nitrobenzyl, p-methoxybenzyl, benzoylmethyl, acetylmethyl, p-nitrobenzoylmethyl, p-bromobenzoylmethyl, p-methanesulfonylbenzoylmethyl, phthalimidomethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2-propenyl, 1,1-dimethylpropyl, acetoxymethyl, propionyloxymethyl, pivaloyloxymethyl, 3-methyl-3-butynyl, succinimidomethyl, 1-cyclopropylethyl, methylsulfenylmethyl, phenylthiomethyl, dimethylaminomethyl, quinoline-1-oxide-2-yl-methyl, pyridine-1-oxide-2-ylmethyl, bis(p-methoxyphenyl)methyl and the like; non-metallic compounds such as titanium tetrachloride; and silyl compounds such as dimethylchlorosilane as mentioned in Japanese Patent Application Kokai (Laid-Open) No. 7,073/71, and Dutch Patent Application No. 71 05259 (Laid-open).

The salts of the compound represented by the formula [I] include conventionally known salts at basic groups, such as amino group and salts at acidic groups, such as carboxyl group. The salts at basic groups include, for example, salts with mineral acids, such as hydrochloric acid, sulfuric acid and the like, salts with organic carboxylic acids such as oxalic acid, formic acid, trichloroacetic acid and trifluoroacetic acid and the like; salts with sulfonic acids such as methanesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid and the like; and salts with amino acids such as aspartic acid, glutamic acid and the like. The salts at acidic groups include, for example, salts with alkali metals such as sodium, potassium and the like; salts with alkaline earth metals such as calcium, magnesium and the like; ammonium salt, salts with nitrogen-containing organic bases such as procain, dibenzylamine, N-benzyl-β-phenethylamine, 1-ephenamine, N,N-dibenzylethylenediamine and the like; and salts with other nitrogen-containing organic bases such as triethylamine, trimethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, diethylamine, dicyclohexylamine and the like.

Moreover, when the compounds represented by the formula [I] and their salts have isomers, for example, optical isomers, geometrical isomers, tautomeric isomers and the like, these isomers are all included in the present invention, and all crystal forms and hydrates are also included in the present invention.

The antibacterial activity and acute toxicity of the representative compounds of this invention are as follows:

1. Antibacterial activity
Test method

According to the standard method of the Nippon Chemotherapy Society [Chemotherapy, Vol. 23, pages 1 to 2 (1975)], a bacterial solution obtained by culturing in Heart Infusion broth (manufactured by Eiken Kagaku) at 37°C for 20 hours was inoculated into a Heart Infusion agar medium (manufactured by Eiken Kagaku) containing a test drug, and subjected to culturing at 37°C for 20 hours, after which the growth of bacteria was observed to determine the minimum concentration at which the growth of bacteria was inhibited, which is expressed as MIC (μg/ml). The amount of bacteria inoculated was 10^4 cells per plate (10^6 cells per ml).

* Penicillinase-producing bacteria
** Cephalospolinase-producing bacteria

MIC values of various compounds of this invention represented by the formula [I] in which R^1 is hydrogen are shown in Table 1.

TABLE 1

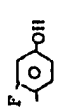
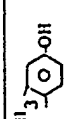
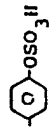
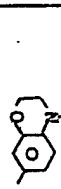
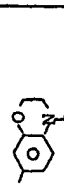
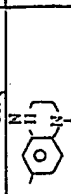
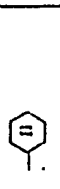
Strain \ Compound	R^2 				
	R^3 				
St. aureus FDA209P	0.39	0.39	0.78	0.78	0.78
E. coli NIHJ JC-2	0.39	0.39	0.39	1.56	1.56
E. coli TK-111	0.2	0.1	0.2	0.78	0.78
Kl. pneumoniae Y-50	0.78	0.39	0.39	3.13	1.56
Kl. pneumoniae Y-41	3.13	3.13	3.13	25	6.25
Ent. cloacae IID977	1.56	0.78	1.56	12.5	3.13
Pro. vulgaris GN3027	0.39	0.39	0.78	1.56	0.2
Pro. morganii T-216	1.56	1.56	3.13	12.5	6.25
Ps. aeruginosa IFO3445	12.5	6.25	25	50	50
Ps. aeruginosa S-68	6.25	6.25	12.5	25	50
Pro. mirabilis T-111	3.13	3.13	3.13	25	12.5
Aci. antitratus A-6	0.78	0.39	1.56	3.13	0.78
St. aureus F-137*	0.39	0.2	0.78	3.13	0.78
E. coli TK-3*	0.78	0.78	0.78	6.25	3.13
E. coli GN5482**	≦0.05	≦0.05	0.1	0.2	0.1
Kl. pneumoniae Y-4*	3.13	3.13	6.25	25	12.5
Pro. vulgaris GN 76**	3.13	3.13	1.56	3.13	3.13
Ps. aeruginosa GN918**	6.25	3.13	3.13	12.5	3.13
Ps. aeruginosa GN3379*	12.5	12.5	25	50	>100

TABLE 1 (cont'd)

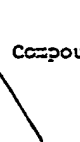
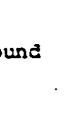
Strain \ Compound	R^2				
	R^3				
St. aureus FDA209P	0.2	0.39	1.56	3.13	0.78
E. coli NIHJ JC-2	0.39	1.56	6.25	3.13	0.78
E. coli TK-111	0.1	0.39	1.56	1.56	0.39
Kl. pneumoniae Y-50	0.39	0.78	1.56	3.13	0.78
Kl. pneumoniae Y-41	1.56	6.25	6.25	25	3.13
Ent. cloacae IID977	0.78	3.13	6.25	12.5	1.56
Pro. vulgaris GN 3027	≦0.05	0.1	0.39	0.78	≦0.05
Pro. morganii T-216	1.56	3.13	3.13	12.5	3.13
Ps. aeruginosa IFO3445	6.25	12.5	12.5	>100	12.5
Ps. aeruginosa S-68	6.25	12.5	12.5	>100	12.5
Pro. mirabilis T-111	1.56	12.5	12.5	25	3.13
Aci. antitratus A-6	0.2	3.13	6.25	6.25	0.78
St. aureus F-137*	0.1	0.39	3.13	3.13	0.39
E. coli TK-3*	0.78	3.13	6.25	12.5	1.56
E. coli GN5482**	0.1	0.39	0.39	1.56	0.2
Kl. pneumoniae Y-4*	1.56	6.25	12.5	25	6.25
Pro. vulgaris GN76**	0.39	0.78	1.56	6.25	0.78
Ps. aeruginosa GN918**	0.78	1.56	1.56	50	3.13
Ps. aeruginosa GN3379*	6.25	12.5	25	>100	25

TABLE 1 (cont'd)

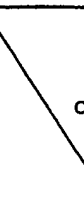
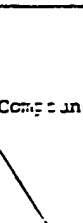
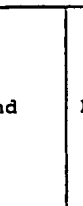
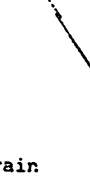
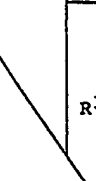
Strain \ Compound	R^2				
	R^3		$-CH=CHCH_3$	$-CH_2CH_2$ 	
St. aureus FDA 209P	0.78	0.78	6.25	0.78	3.13
E. coli NIHJ JC-2	1.56	0.78	3.13	3.13	6.25
E. coli TK-111	0.39	0.2	1.56	0.39	1.56
Kl. pneumoniae Y-50	0.78	0.39	1.56	1.56	3.13
Kl. pneumoniae Y-41	6.25	1.56	12.5	12.5	25
Ent. cloacae IID977	3.13	1.56	6.25	6.25	12.5
Pro. vulgaris GN3027	0.39	0.1	0.39	0.1	0.39
Pro. morganii T-216	3.13	1.56	3.13	3.13	12.5
Ps. aeruginosa IFO3445	25	6.25	25	25	100
Ps. aeruginosa S-68	25	6.25	12.5	12.5	50
Pro. mirabilis T-111	6.25	3.13	25	12.5	25
Aci. antitratus A-6	0.39	0.78	6.25	0.39	–
St. aureus F-137*	0.78	0.78	12.5	0.78	3.13
E. coli TK-3*	3.13	1.56	3.13	3.13	12.5
E. coli GN5482**	0.2	0.1	0.39	0.2	0.78
Kl. pneumoniae Y-4*	12.5	6.25	25	12.5	25
Pro. vulgaris GN76**	1.56	0.78	1.56	1.56	6.25
Ps. aeruginosa GN918**	12.5	3.13	6.25	3.13	12.5
Ps. aeruginosa GN3379*	50	25	25	12.5	100

TABLE 1 (cont'd)

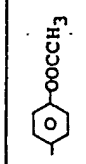
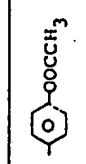
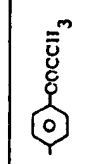
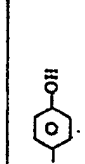
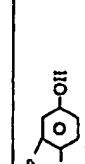
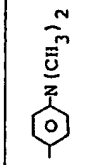
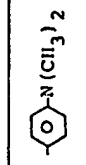
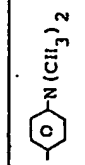
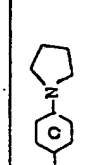
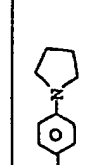
Compound / Strain	R^2 				
	R^3 				
	*1	*2	*3		
St. aureus FDA209P	0.39	0.39	1.56	0.2	≦0.05
E. coli NIHJ JC-2	0.39	0.39	3.13	0.39	0.2
E. coli TK-111	0.2	0.2	0.78	0.2	≦0.05
Kl. pneumoniae Y-50	0.78	0.78	3.13	0.78	0.39
Kl. pneumoniae Y-41	3.13	3.13	25	1.56	1.56
Ent. cloacae IID977	1.56	1.56	6.25	.078	0.78
Pro. vulgaris GN3027	0.39	0.39	0.78	0.2	0.2
Pro. morganii T-216	3.13	3.13	12.5	1.56	0.78
Ps. aeruginosa IFO3445	12.5	12.5	50	6.25	6.25
Ps. aeruginosa S-68	6.25	6.25	25	3.13	3.13
Pro. mirabilis T-111	6.25	6.25	25	1.56	0.78
Aci. antitratus A-6	0.39	0.39	1.56	≦0.05	≦0.05
St. aureus F-137*	0.39	0.39	1.56	0.1	≦0.05
E. coli TK-3*	1.56	1.56	6.25	0.78	–
E. coli GN5482**	≦0.05	≦0.05	0.1	≦0.05	≦0.05
Kl. pneumoniae Y-4*	6.25	6.25	25	3.13	3.13
Pro. vulgaris GN76**	1.56	1.56	6.25	0.78	0.78
Ps. aeruginosa GN918**	3.13	3.13	12.5	1.56	0.78
Ps. aeruginosa GN3379*	12.5	12.5	50	3.13	3.13

TABLE 1 (cont'd)

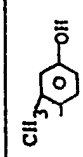
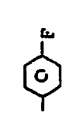
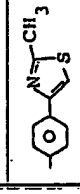
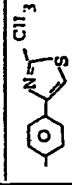
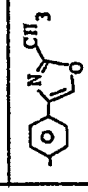
Strain \ Compound	R^2 				
	R^3 				
St. aureus FDA209P	0.39	≦0.05	0.2	0.1	0.39
E. coli NIHJ JC-2	0.1	0.1	1.56	0.1	0.78
E. coli TK-111	≦0.05	≦0.05	0.39	≦0.05	0.39
Kl. pneumoniae Y-50	0.2	0.2	3.13	0.2	1.56
Kl. pneumoniae Y-41	0.78	1.56	6.25	1.56	6.25
Ent. cloacae IID977	0.2	0.39	6.25	0.39	3.13
Pro. vulgaris GN3027	0.39	0.39	1.56	0.39	0.39
Pro. morganii T-216	1.56	1.56	3.13	3.13	6.25
Ps. aeruginosa IFO3445	6.25	3.13	25	3.13	25
Ps. aeruginosa S-68	6.25	3.13	12.5	3.13	12.5
Pro. mirabilis T-111	3.13	0.78	6.25	1.56	6.25
Aci. antitratus A-6	0.78	≦0.05	0.1	0.39	0.2
St. aureus F-137*	0.39	≦0.05	0.2	0.1	0.39
E. coli TK-3*	0.2	0.39	3.13	0.2	3.13
E. coli GN5482**	≦0.05	≦0.05	0.78	≦0.05	0.2
Kl. pneumoniae Y-4*	0.78	1.56	25	3.13	12.5
Pro. vulgaris GN76**	1.56	0.39	3.13	0.78	3.13
Ps. aeruginosa GN918**	3.13	0.39	3.13	0.78	3.13
Ps. aeruginosa GN3379*	6.25	6.25	25	6.25	25

TABLE 1 (cont'd)

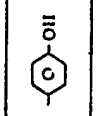
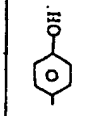
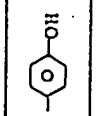
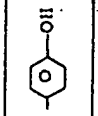
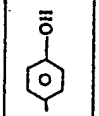
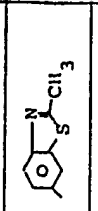
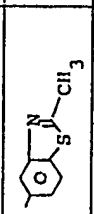
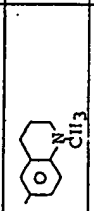
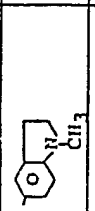
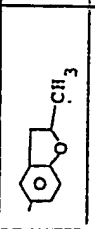
Strain \ Compound	R^2 				
	R^3 				
St. aureus FDA209P	0.39	0.39	0.39	0.2	1.56
E. coli NIHJ JC-2	0.39	0.39	0.39	0.2	1.56
E. coli TK-111	0.2	0.1	0.2	≦0.05	0.78
Kl. pneumoniae Y-50	0.39	0.78	1.56	0.39	1.56
Kl. pneumoniae Y-41	3.13	3.13	3.13	1.56	6.25
Ent. cloacae IID977	1.56	1.56	1.56	0.78	3.13
Pro. vulgaris GN3027	0.39	0.39	0.78	0.2	0.78
Pro. morganii T-216	3.13	3.13	3.13	0.78	3.13
Ps. aeruginosa IFO3445	25	12.5	12.5	12.5	50
Ps. aeruginosa S-68	12.5	6.25	6.25	6.25	25
Pro. mirabilis T-111	3.13	3.13	3.13	3.13	12.5
Aci. antitratus A-6	–	–	0.39	0.39	3.13
St. aureus F-137*	0.39	0.78	0.2	0.1	3.13
E. coli TK-3*	0.78	0.78	1.56	0.39	3.13
E. coli GN5482**	≦0.05	≦0.05	≦0.05	≦0.05	1.56
Kl. pneumoniae Y-4*	3.13	3.13	6.25	1.56	12.5
Pro. vulgaris GN76**	0.78	1.56	1.56	0.39	3.13
Ps. aeruginosa GN918**	1.56	1.56	3.13	1.56	12.5
Ps. aeruginosa GN3379*	12.5	6.25	12.5	6.25	25

TABLE 1 (cont'd)

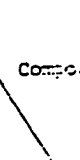
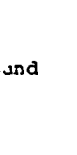
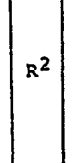
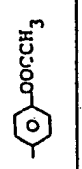
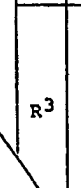
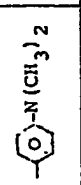
Strain \ Compound						
	R^2					
	R^3					
		*4		*5		*6
St. aureus FDA209P		0.2	≦0.05	0.39	0.2	≦0.05
E. coli NIHJ JC-2		0.2	≦0.05	0.39	0.39	0.1
E. coli TK-111		0.1	≦0.05	0.2	0.2	≦0.05
Kl. pneumoniae Y-50		0.39	0.2	0.78	0.39	0.39
Kl. pneumoniae Y-41		3.13	0.39	3.13	1.56	3.13
Ent. cloacae IID977		0.78	0.39	1.56	0.78	0.78
Pro. vulgaris GN3027		0.2	≦0.05	0.39	≦0.05	0.1
Pro. morganii T-216		1.56	0.39	1.56	0.78	3.13
Ps. aeruginosa IFO3445		12.5	1.56	6.25	12.5	6.25
Ps. aeruginosa S-68		6.25	1.56	3.13	6.25	6.25
Pro. mirabilis T-111		3.13	0.39	3.13	3.13	1.56
Aci. antitratus A-6		0.2	≦0.05	–	0.78	0.39
St. aureus F-137*		0.2	≦0.05	0.39	0.39	≦0.05
E. coli TK-3*		0.78	0.2	1.56	–	0.39
E. coli GN5482**		≦0.05	≦0.05	≦0.05	≦0.05	≦0.05
Kl. pneumoniae Y-4*		3.13	0.78	3.13	3.13	3.13
Pro. vulgaris GN76**		1.56	0.39	3.13	0.78	0.78
Ps. aeruginosa GN918**		1.56	0.78	3.13	1.56	1.56
Ps. aeruginosa GN3379*		6.25	3.13	6.25	6.25	12.5

TABLE 1 (cont'd)

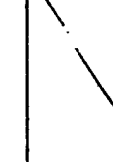
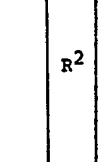
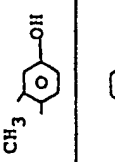
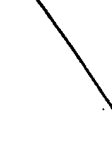
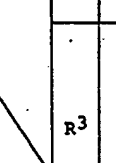
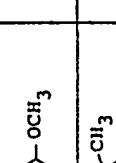
Strain \ Compound	R^2				
	R^3				
St. aureus FDA209P	0.1	0.39	≦0.05	0.39	0.2
E. coli NIHJ JC-2	0.1	0.39	≦0.05	0.39	0.2
E. coli TK-111	0.05	0.1	0.05	0.1	0.1
Kl. pneumoniae Y-50	0.1	0.39	0.2	0.78	0.1
Kl. pneumoniae Y-41	0.78	1.56	0.78	3.13	0.78
Ent. cloacae IID977	0.39	0.78	0.39	1.56	0.39
Pro. vulgaris GN3027	≦0.05	0.39	0.1	0.2	≦0.05
Pro. morganii T-216	1.56	1.56	0.78	1.56	0.39
Ps. aeruginosa IFO3445	3.13	3.13	3.13	12.5	6.25
Ps. aeruginosa S-68	3.13	3.13	3.13	12.5	3.13
Pro. mirabilis T-111	1.56	3.13	0.78	3.13	0.78
Aci. antitratus A-6	0.2	0.78	≦0.05	0.1	0.78
St. aureus F-137*	0.1	0.39	≦0.05	0.39	0.2
E. coli TK-3*	0.2	0.39	0.2	1.56	0.39
E. coli GN5482**	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05
Kl. pneumoniae Y-4*	0.78	1.56	0.78	3.13	1.56
Pro. vulgaris GN76**	0.39	0.78	0.39	0.78	0.2
Ps. aeruginosa GN918**	1.56	0.78	0.39	0.78	1.56
Ps. aeruginosa GN3379*	12.5	6.25	6.25	25	12.5

TABLE 1 (cont'd)

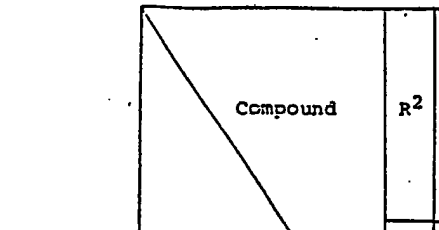
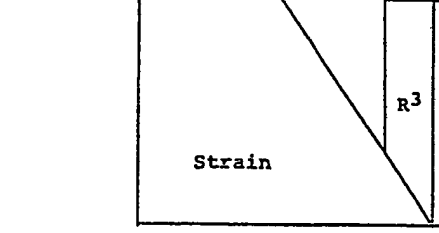
Strain \ Compound	R^2 				
	R^3 				
St. aureus FDA209P	0.1	0.1	0.1	0.1	0.2
E. coli NIHJ JC-2	0.39	0.39	0.39	0.1	0.39
E. coli TK-111	0.1	≦0.05	0.2	≦0.05	≦0.05
Kl. pneumoniae Y-50	0.2	0.78	0.39	0.39	0.78
Kl. pneumoniae Y-41	0.78	1.56	3.13	1.56	3.13
Ent. cloacae IID977	0.78	0.39	1.56	0.78	1.56
Pro. vulgaris GN3027	0.2	0.1	0.1	0.2	0.1
Pro. morganii T-216	1.56	1.56	1.56	1.56	1.56
Ps. aeruginosa IFO3445	6.25	12.5	25	3.13	3.13
Ps. aeruginosa S-68	6.25	6.25	3.13	3.13	3.13
Pro. mirabilis T-111	1.56	1.56	3.13	1.56	3.13
Aci. antitratus A-6	3.13	0.39	0.1	0.1	0.78
St. aureus F-137*	0.1	0.1	0.2	0.1	0.2
E. coli TK-3*	0.39	0.39	0.39	0.39	0.78
E. coli GN5482**	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05
Kl. pneumoniae Y-4*	1.56	1.56	3.13	1.56	3.13
Pro. vulgaris GN76**	0.78	0.39	0.39	0.78	0.78
Ps. aeruginosa GN918**	3.13	1.56	1.56	1.56	1.56
Ps. aeruginosa GN3379*	25	12.5	6.25	3.13	3.13

TABLE 1 (cont'd)

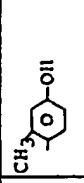
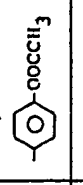
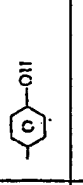
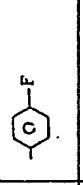
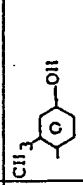
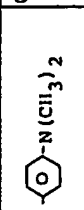
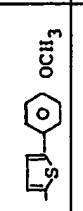
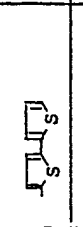
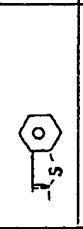
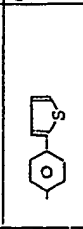
Strain \ Compound						
	R^2					
	R^3					
St. aureus FDA209P		≦0.05	0.1	≦0.05	0.78	≦0.05
E. coli NIHJ JC-2		0.1	0.39	0.2	3.13	0.1
E. coli TK-111		≦0.05	0.2	0.1	0.78	≦0.05
Kl. pneumoniae Y-50		0.2	1.56	0.39	3.13	0.39
Kl. pneumoniae Y-41		0.78	3.13	0.78	6.25	0.78
Ent. cloacae IID977		0.39	3.13	0.39	3.13	0.39
Pro. vulgaris GN3027		0.1	0.39	≦0.05	0.39	≦0.05
Pro. morganii T-216		0.78	1.56	0.78	3.13	0.39
Ps. aeruginosa IFO3445		3.13	3.13	1.56	12.5	6.25
Ps. aeruginosa S-68		3.13	3.13	0.78	6.25	1.56
Pro. mirabilis T-111		0.78	3.13	0.78	3.13	0.39
Aci. antitratus A-6		0.1	0.2	0.2	–	–
St. aureus F-137*		≦0.05	0.1	≦0.05	0.39	≦0.05
E. coli TK-3*		0.2	1.56	0.39	3.13	0.39
E. coli GN5482**		≦0.05	≦0.1	≦0.05	0.39	≦0.05
Kl. pneumoniae Y-4*		0.78	3.13	1.56	12.5	0.78
Pro. vulgaris GN76**		0.39	0.78	0.2	1.56	0.2
Ps. aeruginosa GN918**		1.56	0.78	0.2	1.56	0.78
Ps. aeruginosa GN3379*		3.13	3.13	0.78	12.5	3.13

TABLE 1 (cont'd)

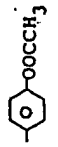
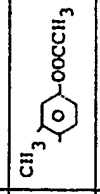
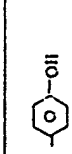
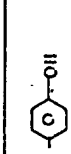
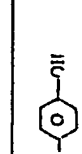
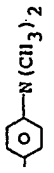
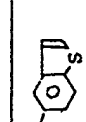
Strain \ Compound						
	R^2					
	R^3					
St. aureus FDA209P		≦0.05	≦0.05	≦0.05	≦0.05	0.2
E. coli NIHJ JC-2		0.2	0.2	0.2	0.39	0.2
E. coli TK-111		≦0.05	≦0.05	0.1	0.1	≦0.05
Kl. pneumoniae Y-50		0.39	0.39	0.39	0.78	0.2
Kl. pneumoniae Y-41		0.78	1.56	1.56	1.56	0.78
Ent. cloacae IID977		0.39	0.78	0.78	0.78	0.78
Pro. vulgaris GN3027		≦0.05	0.39	≦0.1	0.2	≦0.05
Pro. morganii T-216		0.39	1.56	0.78	0.39	0.39
Ps. aeruginosa IFO3445		1.56	6.25	3.13	6.25	1.56
Ps. aeruginosa S-68		1.56	3.13	3.13	3.13	3.13
Pro. mirabilis T-111		0.39	0.78	1.56	0.78	0.78
Aci. antitratus A-6		≦0.05	≦0.05	0.1	0.1	0.1
St. aureus F-137*		≦0.05	≦0.05	≦0.05	≦0.05	0.39
E. coli TK-3*		0.39	0.39	0.78	0.39	0.39
E. coli GN5482**		≦0.05	≦0.05	≦0.05	≦0.05	≦0.05
Kl. pneumoniae Y-4*		1.56	1.56	1.56	1.56	0.78
Pro. vulgaris GN76**		0.39	0.39	0.39	0.39	0.2
Ps. aeruginosa GN918**		1.56	1.56	0.78	0.78	0.39
Ps. aeruginosa GN3379*		3.13	6.25	3.13	3.13	1.56

TABLE 1 (cont'd)

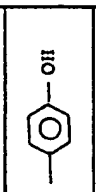
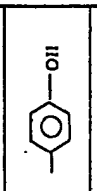
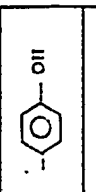
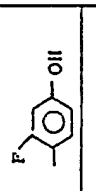
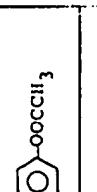
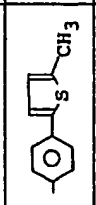
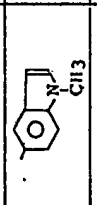
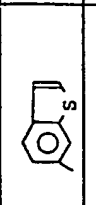
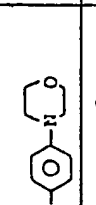
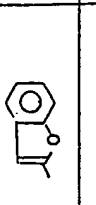
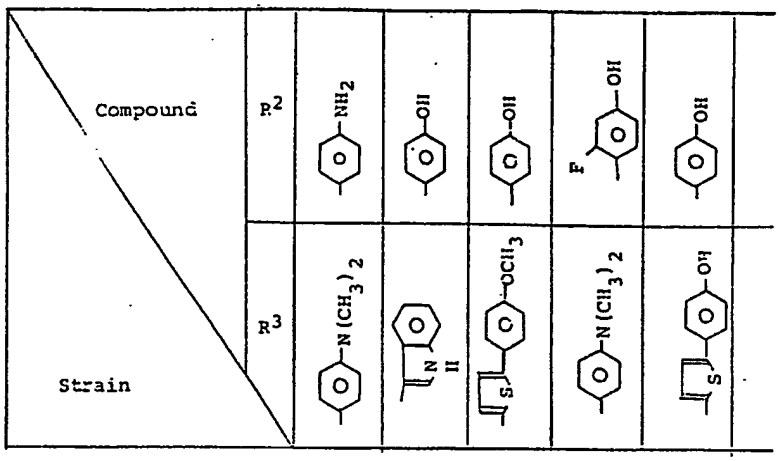
Strain \ Compound	R^2 				
	R^3 				
St. aureus FDA209P	≦0.05	≦0.05	0.1	0.78	0.39
E. coli NIHJ JC-2	0.2	0.1	0.2	1.56	1.56
E. coli TK-111	0.1	≦0.05	≦0.05	0.39	0.78
Kl. pneumoniae Y-50	0.78	0.2	0.39	1.56	0.78
Kl. pneumoniae Y-41	1.56	0.78	0.78	12.5	6.25
Ent. cloacae IID977	0.78	0.39	0.39	6.25	3.13
Pro. vulgaris GN3027	0.1	0.1	≦0.05	1.56	0.39
Pro. morganii T-216	0.78	0.39	0.39	12.5	3.13
Ps. aeruginosa IFO3445	6.25	3.13	1.56	100	6.25
Ps. aeruginosa S-68	3.13	3.13	1.56	25	6.25
Pro. mirabilis T-111	0.39	0.78	1.56	12.5	6.25
Aci. antitratus A-6	≦0.05	0.1	–	6.25	0.78
St. aureus F-137*	≦0.05	≦0.05	0.1	0.78	0.39
E. coli TK-3*	0.39	0.39	0.39	3.13	3.13
E. coli GN5482**	≦0.05	≦0.05	≦0.05	0.39	0.2
Kl. pneumoniae Y-4*	1.56	0.78	1.56	25	12.5
Pro. vulgaris GN76**	0.39	0.39	0.39	6.25	1.56
Ps. aeruginosa GN918**	1.56	0.78	0.78	12.5	–
Ps. aeruginosa GN3379*	6.25	3.13	3.13	50	6.25

TABLE 1 (cont'd)



Strain					
St. aureus FDA209P	3.13	12.5	0.1	≦0.05	0.1
E. coli NIHJ JC-2	0.78	3.13	0.39	0.1	0.39
E. coli TK-111	0.2	3.13	0.1	≦0.05	≦0.05
Kl. pneumoniae Y-50	0.78	3.13	0.78	0.2	0.78
Kl. pneumoniae Y-41	6.25	25	1.56	3.13	3.13
Ent. cloacae IID977	1.56	12.5	0.78	0.2	1.56
Pro. vulgaris GN3027	0.39	1.56	0.2	≦0.05	0.39
Pro. morganii T-216	3.13	12.5	0.78	0.78	1.56
Ps. aeruginosa IFO3445	25	25	3.13	1.56	3.13
Ps. aeruginosa S-68	12.5	100	1.56	1.56	3.13
Pro. mirabilis T-111	6.25	100	1.56	0.78	6.25
Aci. antitratus A-6	0.39	>100	0.39	0.1	0.78
St. aureus F-137*	1.56	50	0.1	≦0.05	0.2
E. coli TK-3*	1.56	6.25	0.78	0.2	0.78
E. coli GN5482**	0.1	0.39	≦0.05	≦0.05	≦0.05
Kl. pneumoniae Y-4*	6.25	50	3.13	0.78	6.25
Pro. vulgaris GN76**	1.56	6.25	0.39	0.2	0.78
Ps. aeruginosa GN918**	–	–	–	–	–
Ps. aeruginosa GN3379*	6.25	50	6.25	3.13	3.13

TABLE 1 (cont'd)

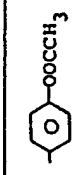
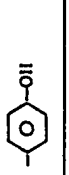
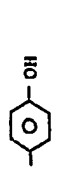
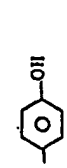
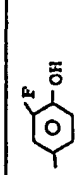
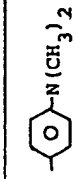
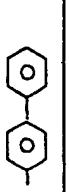
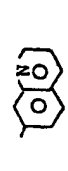
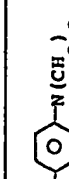
Strain \ Compound						
	R^2					
	R^3					
St. aureus FDA209P		0.1	≦0.05	0.2	1.56	0.39
E. coli NIHJ JC-2		0.2	0.39	0.2	0.78	0.39
E. coli TK-111		≦0.05	0.1	≦0.05	0.39	0.1
Kl. pneumoniae Y-50		0.39	0.39	0.2	1.56	0.39
Kl. pneumoniae Y-41		1.56	12.5	0.78	6.25	3.13
Ent. cloacae IID977		1.56	3.13	0.78	3.13	1.56
Pro. vulgaris GN3027		0.1	0.2	≦0.05	0.39	0.2
Pro. morganii T-216		0.78	1.56	0.39	6.25	1.56
Ps. aeruginosa IFO3445		3.13	25	3.13	25	3.13
Ps. aeruginosa S-68		3.13	12.5	3.13	12.5	1.56
Pro. mirabilis T-111		3.13	3.13	3.13	25	3.13
Aci. antitratus A-6		0.2	0.39	0.39	25	0.39
St. aureus F-137*		0.1	≦0.05	0.2	1.56	0.39
E. coli TK-3*		0.39	0.78	0.2	0.39	0.78
E. coli GN5482**		≦0.05	≦0.05	≦0.05	≦0.05	≦0.05
Kl. pneumoniae Y-4*		3.13	12.5	1.56	12.5	3.13
Pro. vulgaris GN76**		0.39	0.78	0.2	3.13	0.78
Ps. aeruginosa GN918**		0.78	1.56	0.78	3.13	12.5
Ps. aeruginosa GN3379*		3.13	100	3.13	12.5	3.13

TABLE 1 (cont'd)

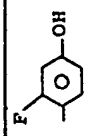
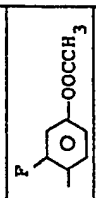
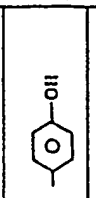
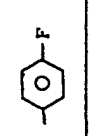
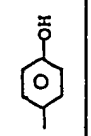
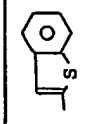
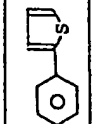
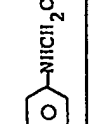
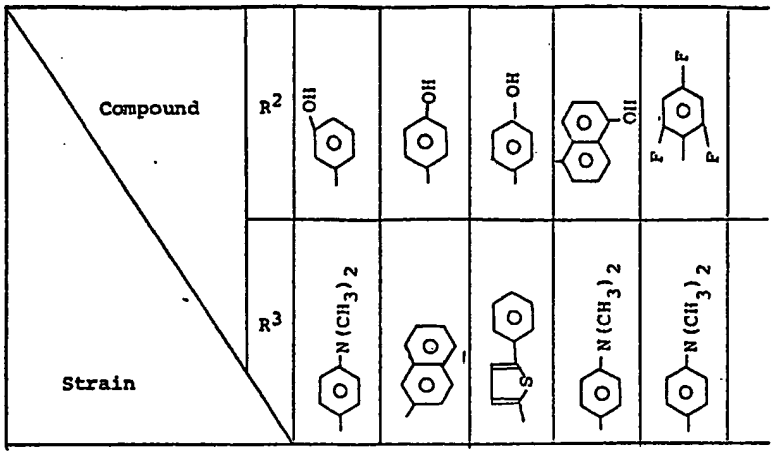
Strain \ Compound	R^2 				
R^3 					
St. aureus FDA209P	≦0.05	0.1	≦0.05	6.25	≦0.05
E. coli NIHJ JC-2	0.2	0.39	0.1	3.13	0.2
E. coli TK-111	≦0.05	≦0.05	≦0.05	1.56	≦0.05
Kl. pneumoniae Y-50	0.2	0.39	0.2	3.13	0.2
Kl. pneumoniae Y-41	1.56	3.13	1.56	12.5	0.78
Ent. cloacae IID977	0.39	0.78	0.39	6.25	0.39
Pro. vulgaris GN3027	≦0.05	0.1	≦0.05	0.78	≦0.05
Pro. morganii T-216	0.78	1.56	0.39	6.25	0.39
Ps. aeruginosa IFO3445	1.56	3.13	1.56	50	3.13
Ps. aeruginosa S-68	1.56	1.56	3.13	12.5	0.78
Pro. mirabilis T-111	0.78	1.56	0.39	50	0.78
Aci. antitratus A-6	0.1	0.2	0.1	12.5	0.2
St. aureus F-137*	≦0.05	≦0.05	≦0.05	6.25	≦0.05
E. coli TK-3*	0.39	0.39	0.39	6.25	0.39
E. coli GN5482**	≦0.05	≦0.05	≦0.05	0.39	≦0.05
Kl. pneumoniae Y-4*	1.56	3.13	0.78	25	0.78
Pro. vulgaris GN76**	0.2	0.39	0.2	3.13	0.2
Ps. aeruginosa GN918**	3.13	6.25	6.25	50	3.13
Ps. aeruginosa GN3379*	1.56	3.13	3.13	25	3.13

TABLE 1 (cont'd)



	St. aureus FDA209P	0.2	≦0.05	≦0.05	0.1	0.78
	E. coli NIHJ JC-2	0.39	0.2	0.39	0.39	1.56
	E. coli TK-111	0.1	≦0.05	≦0.05	≦0.05	0.78
	Kl. pneumoniae Y-50	0.39	0.39	0.78	0.78	3.13
	Kl. pneumoniae Y-41	1.56	1.56	3.13	6.25	12.5
	Ent. cloacae IID977	0.78	0.39	1.56	1.56	6.25
	Pro. vulgaris GN3027	0.2	0.1	≦0.05	1.56	0.39
	Pro. morganii T-216	1.56	0.39	0.78	3.13	6.25
	Ps. aeruginosa IFO3445	12.5	6.25	3.13	12.5	100
	Ps. aeruginosa S-68	6.25	1.56	3.13	12.5	50
	Pro. mirabilis T-111	3.13	0.78	0.78	3.13	12.5
	Aci. antitratus A-6	0.39	0.2	0.2	0.39	0.78
	St. aureus F-137*	0.2	≦0.05	≦0.05	≦0.05	0.78
	E. coli TK-3*	0.39	0.39	0.78	1.56	1.56
	E. coli GN5482**	≦0.05	≦0.05	≦0.05	≦0.05	0.39
	Kl. pneumoniae Y-4*	3.13	1.56	1.56	6.25	12.5
	Pro. vulgaris GN76**	0.78	0.39	0.39	1.56	1.56
	Ps. aeruginosa GN918**	12.5	6.25	1.56	6.25	50
	Ps. aeruginosa GN3379*	6.25	3.13	3.13	>100	50

TABLE 1 (cont'd)

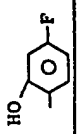
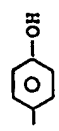
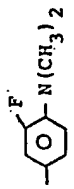
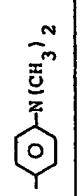
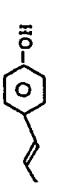
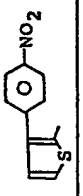
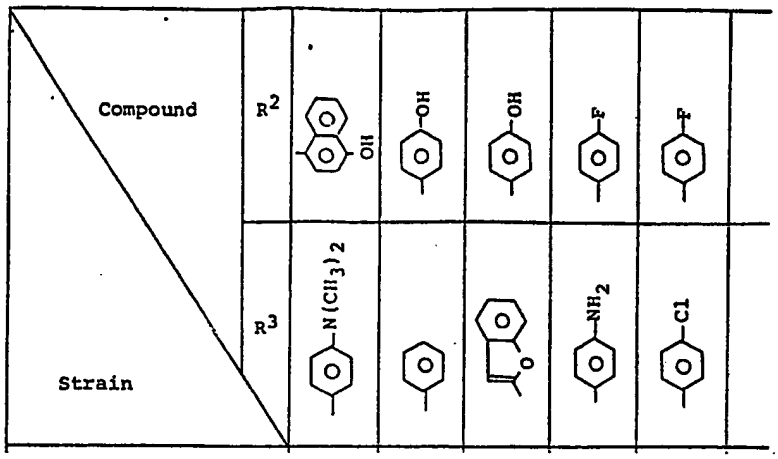
Strain \ Compound		R^2 			
		R^3 			
St. aureus FDA209P		1.56	0.2	0.78	0.2
E. coli NIHJ JC-2		3.13	0.78	6.25	1.56
E. coli TK-111		0.78	1.56	0.78	0.2
Kl. pneumoniae Y-50		3.13	1.56	6.25	1.56
Kl. pneumoniae Y-41		12.5	6.25	25	6.25
Ent. cloacae IID977		6.25	1.56	25	3.13
Pro. vulgaris GN3027		0.78	0.39	0.78	0.39
Pro. morganii T-216		12.5	3.13	6.25	1.56
Ps. aeruginosa IFO3445		50	12.5	50	12.5
Ps. aeruginosa S-68		12.5	12.5	25	12.5
Pro. mirabilis T-111		25	6.25	25	6.25
Aci. antitratus A-6		1.56	0.78	6.25	0.78
St. aureus F-137*		1.56	0.2	0.78	0.1
E. coli TK-3*		6.25	1.56	6.25	3.13
E. coli GN5482**		0.39	≦0.05	0.2	0.2
Kl. pneumoniae Y-4*		25	6.25	25	6.25
Pro. vulgaris GN76**		3.13	1.56	6.25	3.13
Ps. aeruginosa GN918**		50	50	25	12.5
Ps. aeruginosa GN3379*		50	25	25	25

TABLE 1 (cont'd)



St. aureus FDA209P	0.78	0.78	0.2	3.13	6.25
E. coli NIHJ JC-2	3.13	0.78	0.78	0.78	3.13
E. coli TK-111	0.39	0.39	0.39	0.39	1.56
Kl. pneumoniae Y-50	1.56	0.39	0.39	0.39	3.13
Kl. pneumoniae Y-41	12.5	6.25	3.13	3.13	12.5
Ent. cloacae IID977	3.13	1.56	1.56	1.56	6.25
Pro. vulgaris GN3027	3.13	0.1	0.1	0.2	0.39
Pro. morganii T-216	12.5	0.78	1.56	1.56	6.25
Ps. aeruginosa IFO3445	50	6.25	6.25	6.25	>100
Ps. aeruginosa S-68	50	6.25	1.56	12.5	50
Pro. mirabilis T-111	12.5	3.13	3.13	6.25	12.5
Aci. antitratus A-6	0.78	3.13	0.78	3.13	3.13
St. aureus F-137*	0.39	1.56	0.39	3.13	6.25
E. coli TK-3*	3.13	1.56	0.78	0.78	6.25
E. coli GN5482**	0.1	0.1	≦0.05	0.2	0.39
Kl. pneumoniae Y-4*	12.5	6.25	6.25	6.25	25
Pro. vulgaris GN76**	3.13	0.39	0.39	0.78	3.13
Ps. aeruginosa GN918**	50	12.5	6.25	3.13	100
Ps. aeruginosa GN3379*	>100	12.5	3.13	25	50

TABLE 1 (cont'd)

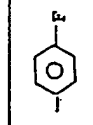
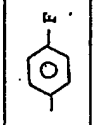
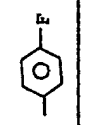
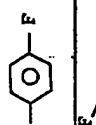
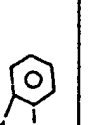
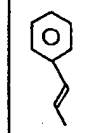
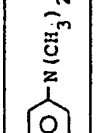
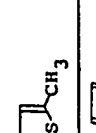
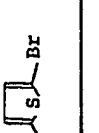
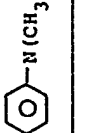
Strain \ Compound	R^2 				
	R^3 				
St. aureus FDA209P	3.13	0.78	3.13	1.56	1.56
E. coli NIHJ JC-2	3.13	0.78	1.56	3.13	1.56
E. coli TK-111	1.56	0.39	0.78	1.56	0.78
Kl. pneumoniae Y-50	6.25	1.56	3.13	3.13	3.13
Kl. pneumoniae Y-41	12.5	6.25	6.25	12.5	6.25
Ent. cloacae IID977	12.5	3.13	3.13	12.5	6.25
Pro. vulgaris GN3027	0.78	0.39	0.2	0.39	0.78
Pro. morganii T-216	12.5	3.13	3.13	6.25	6.25
Ps. aeruginosa IFO3445	50	25	50	50	>100
Ps. aeruginosa S-68	25	12.5	25	25	25
Pro. mirabilis T-111	12.5	6.25	6.25	12.5	25
Aci. antitratus A-6	1.56	0.39	1.56	1.56	1.56
St. aureus F-137*	3.13	0.78	3.13	3.13	1.56
E. coli TK-3*	12.5	3.13	3.13	6.25	3.13
E. coli GN5482**	0.39	0.2	0.2	0.39	0.39
Kl. pneumoniae Y-4*	25	12.5	12.5	25	25
Pro. vulgaris GN76**	3.13	1.56	1.56	3.13	3.13
Ps. aeruginosa GN918**	50	12.5	50	100	>100
Ps. aeruginosa GN3379*	25	12.5	25	25	>100

TABLE 1 (cont'd)

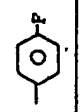
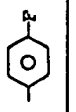
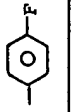
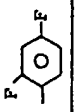
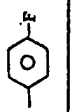
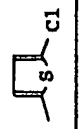
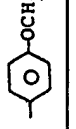
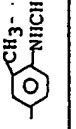
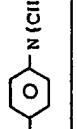
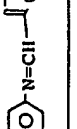
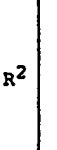
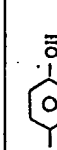
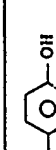
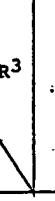
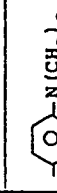
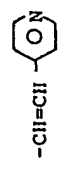
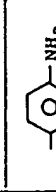
Strain \ Compound	R^2 				
	R^3 				
St. aureus FDA209P	3.13	3.13	1.56	0.2	6.25
E. coli NIHJ JC-2	3.13	1.56	1.56	0.78	1.56
E. coli TK-111	1.56	0.78	0.39	0.2	0.78
Kl. pneumoniae Y-50	3.13	3.13	1.56	0.78	1.56
Kl. pneumoniae Y-41	12.5	12.5	6.25	6.25	6.25
Ent. cloacae IID977	12.5	6.25	6.25	3.13	6.25
Pro. vulgaris GN3027	0.39	0.39	0.78	0.2	0.39
Pro. morganii T-216	6.25	6.25	6.25	3.13	3.13
Ps. aeruginosa IFO3445	50	25	50	12.5	25
Ps. aeruginosa S-68	25	25	12.5	12.5	25
Pro. mirabilis T-111	12.5	12.5	12.5	3.13	12.5
Aci. antitratus A-6	1.56	1.56	0.78	0.39	3.13
St. aureus F-137*	3.13	3.13	0.78	0.1	6.25
E. coli TK-3*	6.25	3.13	3.13	3.13	3.13
E. coli GN5482**	0.39	0.2	0.2	0.1	0.39
Kl. pneumoniae Y-4*	25	12.5	12.5	6.25	25
Pro. vulgaris GN76**	3.13	3.13	3.13	0.78	1.56
Ps. aeruginosa GN918**	100	50	50	12.5	25
Ps. aeruginosa GN3379*	25	25	25	25	50

TABLE 1 (cont'd)

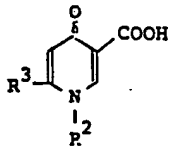
Strain \ Compound	R^2 			
R^3				
St. aureus FDA209P	3.13	0.2	12.5	3.13
E. coli NIHJ JC-2	1.56	0.2	0.78	1.56
E. coli TK-111	0.78	0.05	0.39	0.78
Kl. pneumoniae Y-50	0.78	0.2	0.78	3.13
Kl. pneumoniae Y-41	6.25	0.78	6.25	12.5
Ent. cloacae IID977	3.13	0.39	3.13	12.5
Pro. vulgaris GN3027	0.39	0.1	0.2	0.39
Pro. morganii T-216	6.25	0.78	6.25	3.13
Ps. aeruginosa IFO3445	25	3.13	50	25
Ps. aeruginosa S-68	12.5	3.13	12.5	25
Pro. mirabilis T-111	12.5	1.56	12.5	25
Aci. antitratus A-6	3.13	0.39	12.5	25
St. aureus F-137*	3.13	0.1	12.5	6.25
E. coli TK-3*	3.13	0.39	1.56	3.13
E. coli GN5482**	0.2	0.05	0.2	0.1
Kl. pneumoniae Y-4*	6.25	1.56	6.25	12.5
Pro. vulgaris GN76**	1.56	0.39	0.78	1.56
Ps. aeruginosa GN918**	12.5	1.50	25	25
Ps. aeruginosa GN3379*	25	3.13	25	25

Note: *1: DL-glutamic acid salt of 2-dimethylaminoethyl ester
*2: L-aspartic acid salt of 2-dimethylaminoethyl ester
*3: 2,3-Dihydroxy-n-propyl ester
*4: 2-Dimethylaminoethyl ester
*5: Methoxymethyl ester
*6: 2-Dimethylaminoethyl ester

2. *Acute toxicity test*

The LD_{50} values of the representative compounds of this invention when administered intravenously to mice (ICR strain, male, 18-24 g) are shown in Table 2.

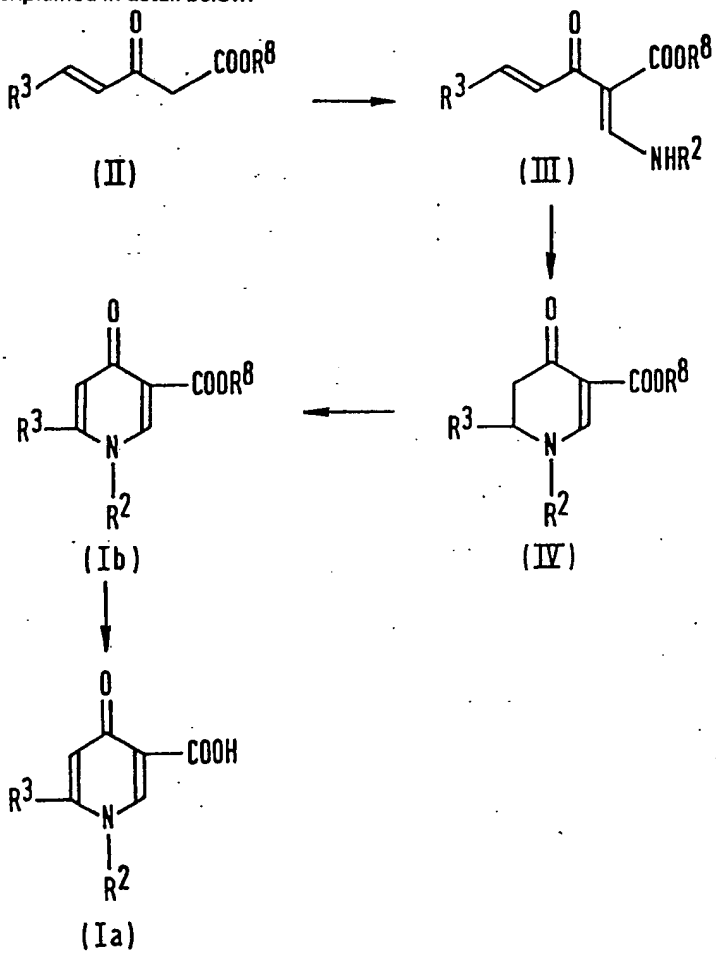
TABLE 2



R^3	R^2	LD_{50} (mg/kg)
-CH=CH-(N)	-F	> 200
-N(CH$_3$)$_2$	-OH	> 200
-NHCH$_2$CH$_2$OH	-F	> 200
-H	H$_3$C, -OH	> 200

Next, the process for producing the compound of this invention is explained below.

The compound of this invention can be produced in the manner known per se, and a representative production process is explained in detail below.



In the above formulas, R^2 and R^3 have the same meanings as defined above, and R^8 represents a carboxyl-protecting group as explained for R^1.

The compound represented by the formula [II] can be produced by a conventional method, for example, the Wittig reaction using a corresponding R^3CHO as the starting material. This compound is reacted with N,N-dimethylformamidodimethylacetal or N,N-dimethylformamidedodiethylacetal, and thereafter, the reaction product is reacted with R^2NH_2 to obtain a compound represented by the formula [III]. The solvent which are used in this reaction may be any solvent inert to the reaction, for example, an aromatic hydrocarbon such as benzene, toluene, xylene or the like; an ether such as dioxane, tetrahydrofuran, anisole, diethyleneglycol dimethyl ether, dimethyl Cellosolve (RTM) or the like; a halogenated hydrocarbon, such as methylene chloride, chloroform, dichloroethane or the like; an amide such as N,N-dimethylformamide, N,N-dimethylacetamide or the like; or a sulfoxide such as dimethylsulfoxide or the like. The amount of the acetal used is preferably 1 mole or more, more preferably 1.0 to 1.2 moles, per mole of the compound represented by the formula [II], and this reaction is usually completed at a temperature of 0°C to 80°C in a period of 10 minutes to 10 hours. In order to subsequently react the product with R^2NH_2, the same solvent as mentioned above is used, and the amine is used in an amount of one mole per mole of the compound represented by the formula [II]. The reaction is conducted at a temperature of 0°C to 100°C for a period of 30 minutes to 10 hours.

As an alternative method, there is a method which comprises reacting the compound represented by the formula [II] with ethyl orthoformate or methyl orthoformate in acetic anhydride, and thereafter, reacting the product with R^2NH_2 to obtain the compound represented by the formula [III]. In this case, the orthoformic acid ester is used in an amont of one more or more, preferably 1.0 to 1.2 moles, per mole of the compound represented by the formula [II] and the reaction is conducted at a temperature of 20°C to 100°C for a period of 5 minutes to 10 hours. Subsequently, the reaction product is reacted with R^2NH_2 in a proportion of one more or more, preferably 1.0 to 1.2 moles, per mole of the compound represented by the formula [II], in the presence of the above-mentioned solvent or in the absence of any solvent, to obtain the compound represented by the formula [III].

The compound represented by the formula [IV] is produced by subjecting the compound represented by the formula [III] to ring-closure reaction. This reaction is conducted in the presence or absence of a solvent such as an amide, for example, N,N-dimethylformamide, N,N-dimethylacetamide or the like, a sulfoxide, for example, dimethylsulfoxide or the like; or a phosphoric acid ester, for example, ethyl polyphosphate or the like, and is preferably completed at a temperature of 50°C to 150°C for a period of 1 hour to 10 hours.

Further, the compound represented by the formula [Ib] is produced by reacting the compound represented by the formula [IV] with a dehydrogenating agent. As this dehydrogenating agent, there may be used all dehydrogenating agents which can conventionally be used, preferably 2,3-dichloro-5,6-dicyano-p-benzoquinone, 2,3,5,6-tetrachloro-p-benzoquinone, 3,4,5,6-tetrachloro-o-benzoquinone or the like, and this dehydrogenating agent may be used in a proportion of one more or more, preferably 1.0 to 1.2 moles, per mole of the compound represented by the formula [IV]. This reaction is usually conducted in a solvent, and preferable examples of the solvent are aromatic hydrocarbons, such as benzene, toluene, xylene and the like; and ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol dimethyl ether, dimethyl Cellosolve and the like. Said reaction is completed at a temperature of 0°C to 100°C in a period of 1 minute to 10 hours.

The compound thus obtained is hydrolyzed by a conventional method, for example, hydrolyzed at a temperature of 0°C to 100°C for a period of 5 minutes to 10 hours in the presence of an alkali or an acid, thereby obtaining the compound represented by the formula [Ia].

In producing the compounds represented by the formula [Ia] or [Ib] via the above-mentioned reaction route, the compound represented by the formula [III] and/or the compound represented by the formula [IV] can be subjected to the subsequent reaction without being isolated.

When the compounds represented by the formula [II], [III], [IV] and [Ib] have active groups, for example, hydroxyl group, amino group, carboxyl group or the like in other sites than the reactive sites, the active groups are previously protected by a protecting group in a conventional manner, and the protecting group is removed after the completion of the reaction in a conventional manner to produce the above compounds.

The compounds thus produced may be, if desired, subjected to a reaction known per se, such as halogenation, esterification, amidation, ureidation, alkylation, alkenylation, alkylidenation, acylation, hydroxylation, iminomethylation, reduction or the like, to derive other compounds therefrom, and hence, have uses as intermediates.

When the compound of this invention is used as a medicine the compound is formed into tablet, capsule, powder, syrup, granule, suppository, ointment, injection or the like in a conventional manner using a proper carrier which is usually used in the formation of a preparation. The administration method, dose and administration time may be varied depending upon symptoms of patients, and usually, the compound may be administered to an adult orally or parenterally (administration by injection or administration to rectal region) in a dose of 0.1 to 100 mg/Kg/day in terms of the compound represented by the formula [I] at one time or in several portions.

This invention is further explained in more detail below referring to Referential Examples, Examples and Preparation Examples.

Referential Example 1

In 20 ml of methanol were dissolved 1.6 g of benzo[b]thiophene-2-aldehyde and 5.1 g of [2-methoxy-3-(methoxycarbonyl)allyl]triphenylphosphonium bromide, and to this solution was added dropwise 2.1 g of a 28% by weight solution of sodium methoxide in methanol with stirring at room temperature over 10 minutes. This mixture was further reacted at the same temperature for 20 minutes, and the solvent was then removed by distillation under reduced pressure. To the residue was added 20 ml of water, and the resulting mixture was extracted with 20 ml of chloroform. The extract was dried with anhydrous magnesium sulfate and the solvent was removed by distillation under reduced pressure. The residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: benzene/n-hexane (3:1 by volume) mixture) to obtain an oily substance. This oily substance was dissolved in 12 ml of dioxane, and to the resulting solution was added 12 ml of 0.1 N sulfuric acid. The resulting mixture was subjected to reaction at 100°C for 1.5 hours. This reaction mixture was then cooled to room temperature and 20 ml of water was added thereto, after which the precipitated crystals were collected by filtration. These crystals were washed with water and then dried to obtain 1.1 g of methyl 5-(2-benzo[b]thienyl)-3-oxo-4-pentenoate having a melting point of 105-107°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1625.

The compounds shown in Table 3 were obtained in the same manner.

TABLE 3

$R^3CH=CHCOCH_2COOCH_3$

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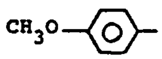	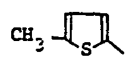	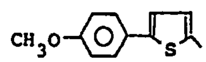
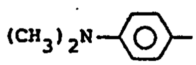	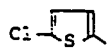	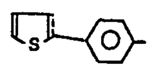
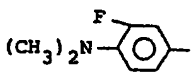	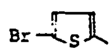	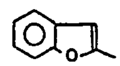
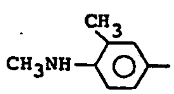	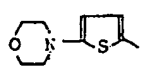	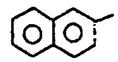
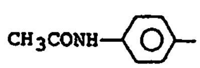	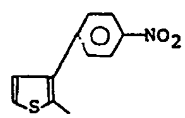	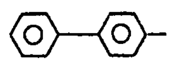
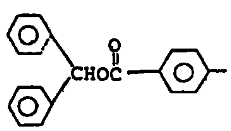	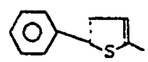	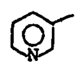
	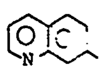	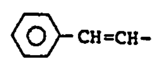
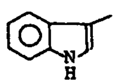	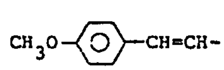	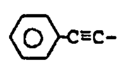
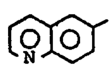	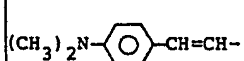	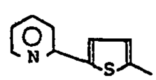
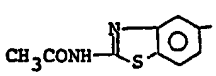	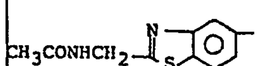	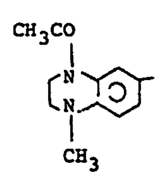
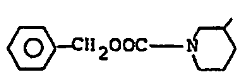	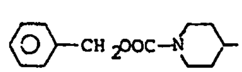	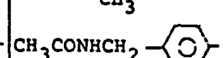

TABLE 3 (cont'd)

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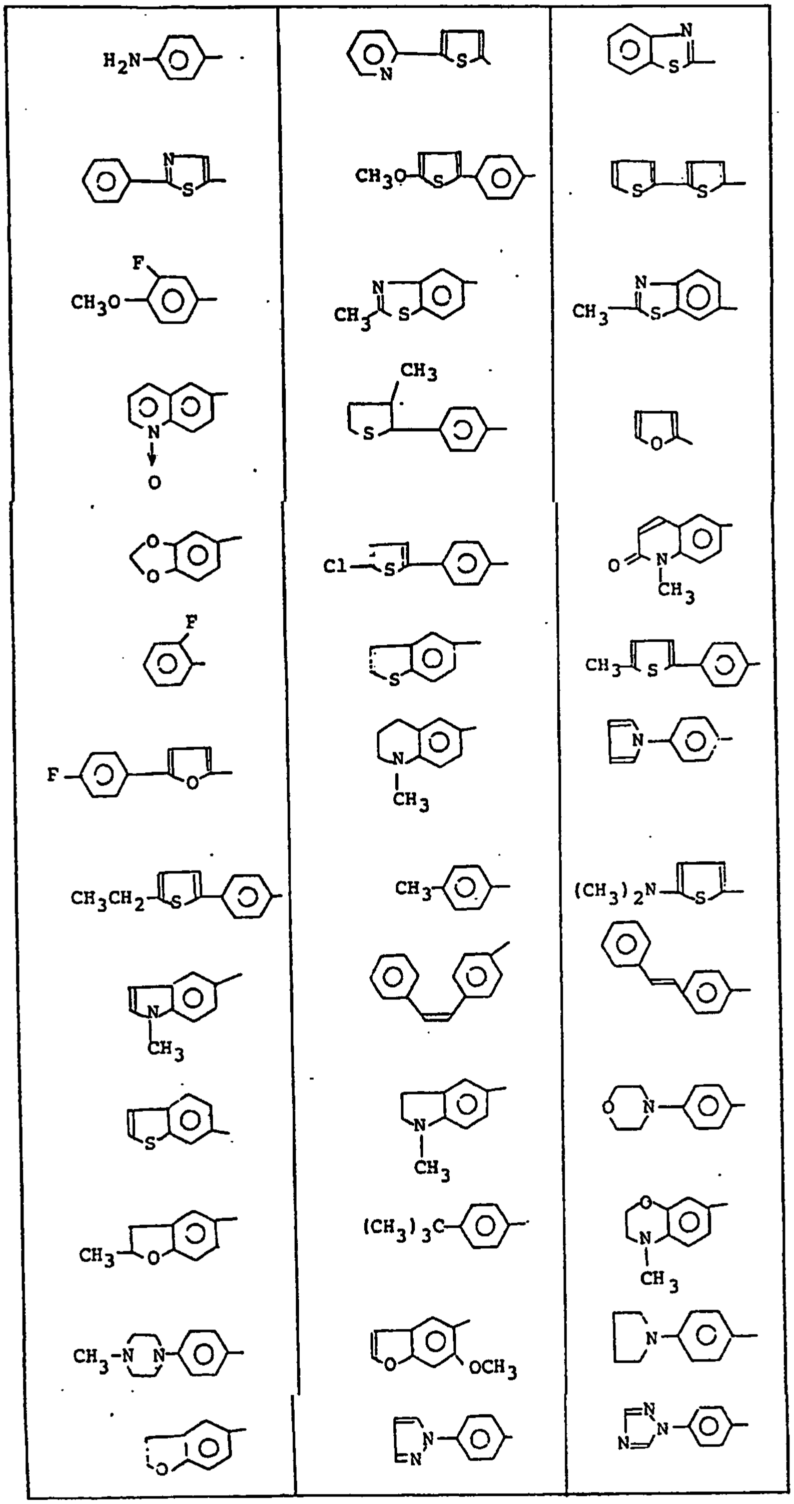

TABLE 3 (cont'd)

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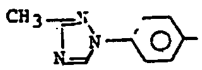
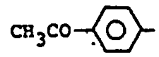
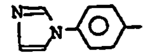
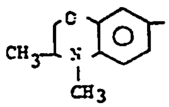
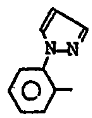
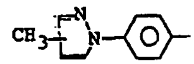
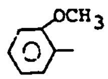
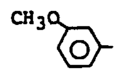
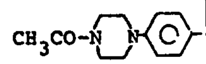
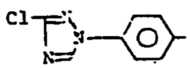
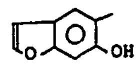
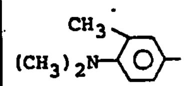
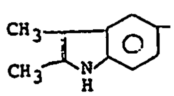
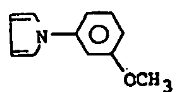
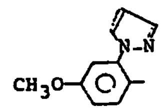
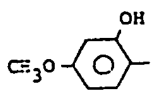
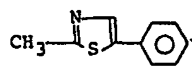
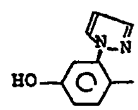
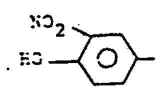
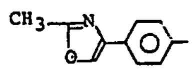
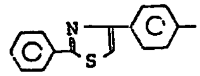
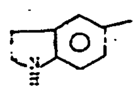
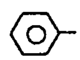
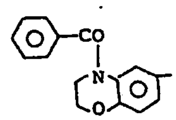
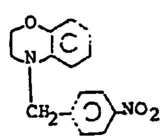
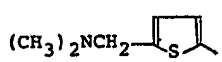
		
		
		
		
		
		
		
		
		

Referential Example 2

In 100 ml of methanol was dissolved 25.7 g of [2-methoxy-3-(methoxycarbonyl)allyl]triphenylphosphonium bromide, and to this solution was added dropwise 10.5 g of a 28% by weight solution of sodium methoxide in methanol with stirring at room temperature over 10 minutes. To the mixed solution was then further added 5 g of 1,2,3,6-tetrahydrobenzaldehyde at room temperature and the resulting mixture was subjected to reaction at the same temperature for 2 hours. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and to the residue was added 50 ml of water. The resulting mixture was extracted with 50 ml of chloroform. The extract was dried with anhydrous magnesium sulfate, and the solvent was then removed by distillation under reduced pressure. The residue was purified by a column chromatography (Wako Silica Gel C-200; eluant: benzene/n-haxane (3:1 by volume) mixture) to obtain an oily substance. This oily substance was dissolved in 100 ml of dioxane, and to the solution was then added 100 ml of 0.1 N sulfuric acid. The resulting mixture was subjected to reaction at 100°C for 1.5 hours. The solvent was then removed by distillation under reduced pressure, and to the residue was added 100 ml of chloroform. The resulting mixture was washed with 100 ml of water. The organic layer was separated, and dried with anhydrous magnesium sulfate and then the solvent was removed by distillation under reduced pressure. The residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: benzene/n-hexane (3:1 by volume) mixture) to obtain 7.5 g of oily methyl 5-(cyclohexen-4-yl)-3-oxo-4-pentenoate.

IR(neat) cm^{-1}: $\nu_{C=O}$ 1740

The compounds shown in Table 4 were obtained in the same manner.

Example 1

(1) In 10 ml of benzene was dissolved 2.0 g of methyl 5-(4-chlorophenyl)-3-oxo-4-pentenoate, and to this solution was added 1.2 g of N,N-dimethylformamidodimethylacetal. The resulting mixture was subjected to reaction at 70°C for 1.5 hours. The reaction mixture was cooled to room temperature, and 1.12 g of p-fluoroaniline was then added thereto, after which the resulting mixture was further subjected to reaction for 1.5 hours. After completion of the reaction, 10 ml of diethyl ether was added to the reaction mixture, and the precipitated crystals were collected by filtration, and washed with 10 ml of diethyl ether to obtain 2.2 g of methyl 5-(4-chlorophenyl)-2-(4-fluorophenylaminomethylene)-3-oxo-4-pentenoate having a melting point of 166 - 168°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1700.

The compounds shown in Table 5 were obtained in the same manner.

TABLE 4

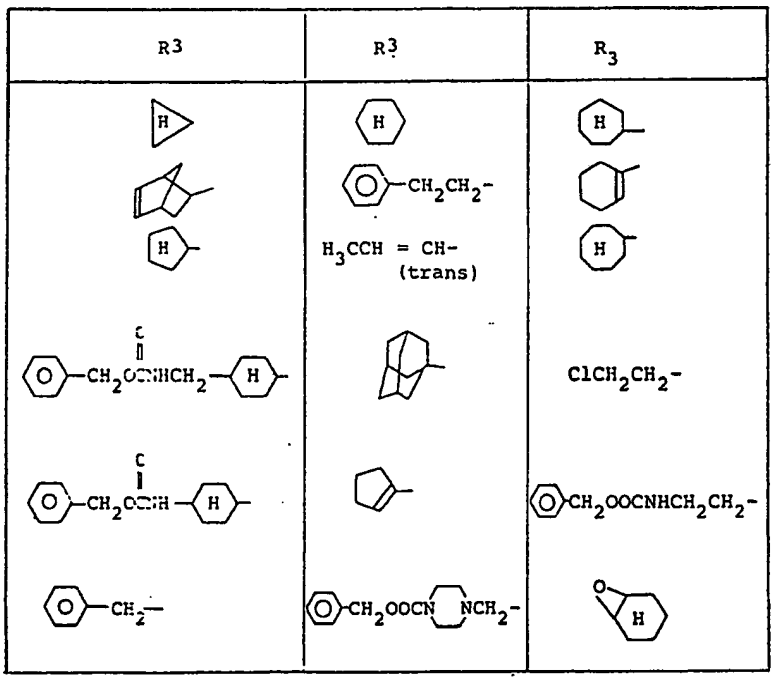
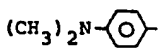
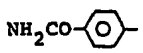
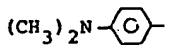
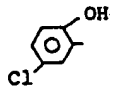
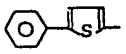
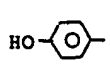
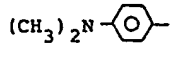
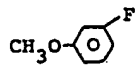
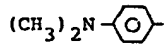
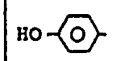
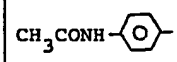
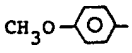
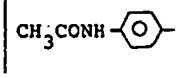
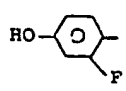
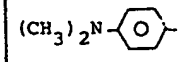
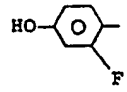


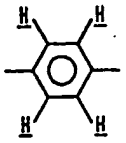
TABLE 5

$R^3CH = CHCOC(COOCH_3) = CHNHR^2$

R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		133 - 136	1680
		235 - 236	1685
		214 - 217	1705
		160 - 165	1690
		193 - 195	1690
		185 - 187	1690
		201 - 203	1700, 1660
		194 - 195	1685
		196 - 197	1690, 1665
		170 - 172	1690, 1660

(2) In 15 ml of N,N-dimethylformamide was dissolved 2.0 g of methyl 5-(4-chlorophenyl)-2-(4-fluorophenylaminomethylene)-3-oxo-4-pentenoate, and they were reacted at 140°C for 4 hours. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: benzene/ethyl acetate (3:1 by volume) mixture) to obtain 1.1 g of oily methyl 6-(4-chlorophenyl)-1-(4-fluorophenyl)-4-oxo-1,4,5,6-tetrahydronicotinate.

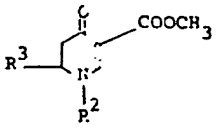
IR (neat) cm^{-1}: $\nu_{C=O}$ 1725
NMR ($CDCl_3$) δ values:
2.5 – 3.5 (2H, m, C_5-H),
3.80 (3H, s, $-COOCH_3$),
5.30 (1H, m, C_6–H),
7.0 – 7.5 (8H, m,



× 2),
8.65 (1H, s, C_2–H)

The compounds shown in Table 6 were obtained in the same manner.

TABLE 6



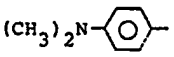
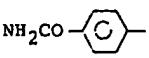
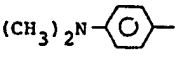
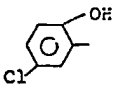
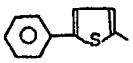
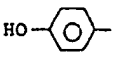
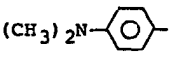
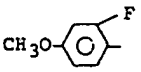
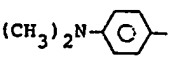
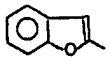
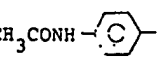
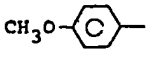
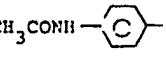
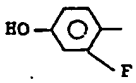
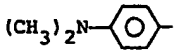
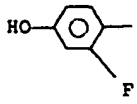
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		145 - 148	1720, 1660
		202 - 205	1730, 1700
		210 - 212	1720
		Oily substance	1720 [neat]
		-	1690
		102 - 110 (decomp.)	1725, 1710
		128 - 131	1710, 1665
		128 - 131	1720,1710 1660

TABLE 6 (cont'd)

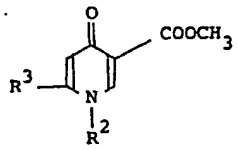
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		-	1720, 1710
		-	1715

(3) In 20 ml of benzene was dissolved 1.0 g of methyl 6-(4-chlorophenyl)-1-(4-fluorophenyl)-4-oxo-1,4,5,6-tetrahydronicotinate, and to the resulting solution was added a mixed solution of 0.7 g of 2,3-dichloro-5,6-dicyano-p-benzoquinone and 5 ml of benzene at 80°C, after which they were reacted at the same temperature for 30 minutes. After completion of the reaction, the solvent was removed from the reaction mixture by distillation under reduced pressure, and the residue was suspended in 30 ml of chloroform and 30 ml of water. This suspension was adjusted to a pH of 7.5 with sodium hydrogencarbonate, and the organic layer was then separated and washed successively with 30 ml of water and 30 ml of a saturated aqueous solution of sodium chloride, and then dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain 0.85 g of methyl 6-(4-chlorophenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinate having a melting point of 250 – 254°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1735.

The compounds shown in Table 7 were obtained in the same manner.

TABLE 7



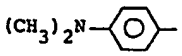
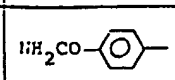
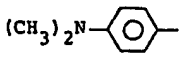
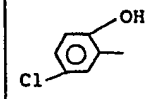
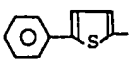
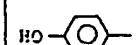
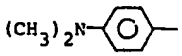
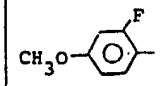
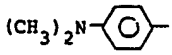
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		153 - 155	1725, 1670
		192 - 196	1730, 1710
		>250	1700
		108 - 110	1730, 1700
		-	1725, 1700

TABLE 7 (cont'd)

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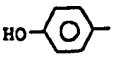
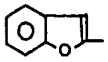
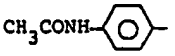
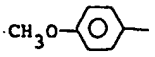
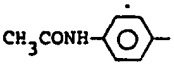
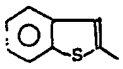
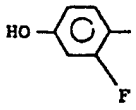
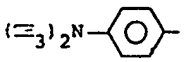
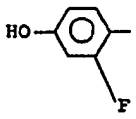
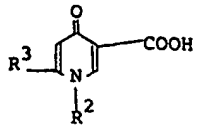
		>250	1730, 1690
		>250	1710, 1680
		189 - 191	1730, 1700, 1670
		>250	1730, 1700
		>250	1725, 1705

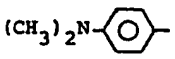
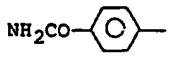
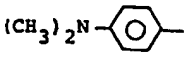
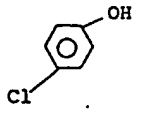
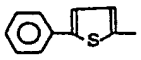
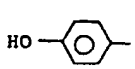
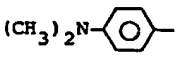
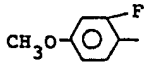
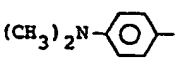
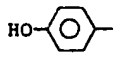
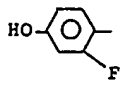
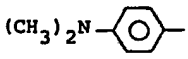
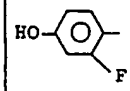
(4) In a mixed solvent of 5 ml of methanol and 5 ml of 1 N aqueous sodium hydroxide solution was dissolved 0.5 g of methyl 6-(4-chlorophenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinate, and they were reacted at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was adjusted to a pH of 5.5 with acetic acid, and the precipitated crystals were collected by filtration, washed with 10 ml of water and dried to obtain 0.4 g of 6-(4-chlorophenyl)-1-(4-fluorophenyl)-4-oxo1,4-dihydronicotinic acid having a melting point of 199 – 204°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1725.

The compounds shown in Table 8 were obtained in the same manner.

TABLE 8



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		278 - 280	1720, 1680 1665
		>250	1720
		>250	1750
		173 - 180	1720
		268 - 271	1720, 1700
		>250	1715
		>250	1720
		>250	1720

Example 2

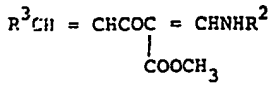
(1) In 25 ml of methylene chloride were dissolved 3.1 g of 2-naphthaldehyde and 9.4 g of [2-methoxy-3-(methoxycarbonyl)allyl]triphenylphosphonium bromide, followed by addition thereto of 19 ml of a 50% by weight aqueous sodium hydroxide solution with stirring at room temperature, and the mixture was subjected to reaction at the same temperature for 20 minutes. After completion of the reaction, the methylene chloride layer was separated from the reaction mixture and washed with water. It was then dried with anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure. To the residue was added 30 ml of diethyl ether, and the insolubles were removed by filtration, after which the filtrate was concentrated to obtain an oily substance. This oily substance was dissolved in a mixed solvent of 45 ml of dioxane and 40 ml of 0.1 N sulfuric acid, and the solution was refluxed for 30 minutes. Then the reaction mixture was cooled to room temperature, extracted with 100 ml of ethyl acetate and the extract was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure, and the formed crystals were suspended in 50 ml of benzene, and to the suspension was added 2.4 g of N,N-dimethylformamidodimethylacetal, and the resulting mixture was subjected to reaction at 60°C for 30 minutes. The reaction mixture was cooled to room temperature, and 2.2 g of p-aminophenol was added thereto. The mixture was subjected to reaction at the same temperature for 2 hours.

The precipitated crystals were collected by filtration, washed with 5 ml of benzene and dried to obtain 1.7 g of methyl 2-(4-hydroxyphenylaminomethylene)-5-(2-naphthyl)-3-oxo-4-pentenoate having a melting point of 191-192.5°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1710.

The compounds shown in Table 9 were obtained in the same manner.

TABLE 9



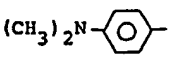
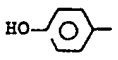
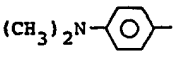
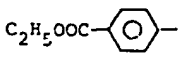
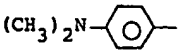
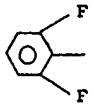
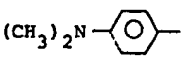
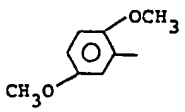
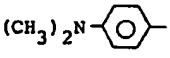
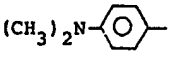
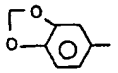
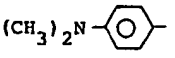
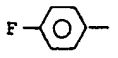
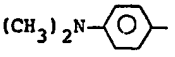
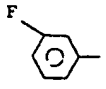
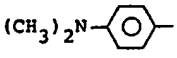
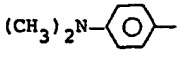
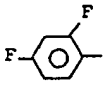
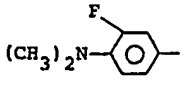
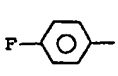
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		172 - 175	1685
		153 - 159	1720, 1705
		146 - 148	1700
		157 - 159	1700, 1685
		199 - 201	1685
		195 - 196	1700
		131 - 133	1685
		141 - 143	1705
		141 - 142	1690
		167 - 168	1700
		118 - 120	1690

TABLE 9 (cont'd)

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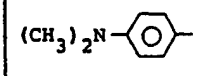
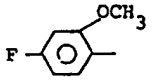
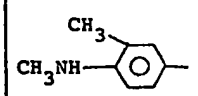
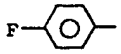
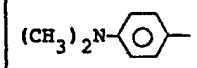
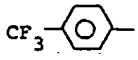
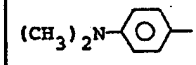
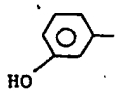
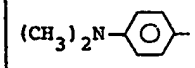
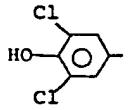
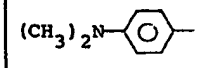
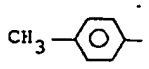
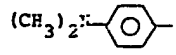
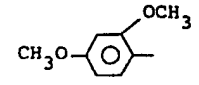
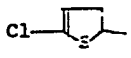
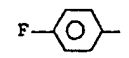
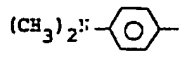
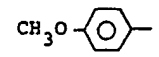
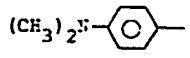
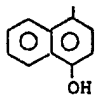
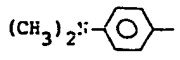
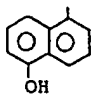
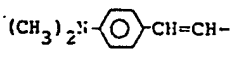
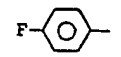
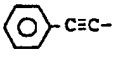
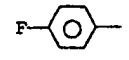
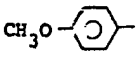
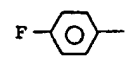
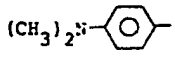
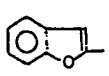
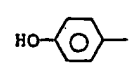
		156 - 158	1685
		134 - 135	1675
		173 - 175	1705
		156 - 158	1670
		189 - 191	1685
		153 - 154	1695
		154 - 156	1680
		152 - 153	1700
		154 - 157	1690
		188 - 190	1700
		234 - 236	1695
		166 - 168	1710, 1695
		149 - 151	2190 ($\nu_{C\equiv C}$), 1705
		128 - 131	1730
		153 - 155	1690
		220 - 222	1710

TABLE 9 (cont'd)

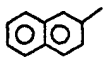
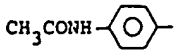
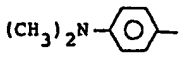
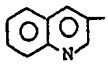
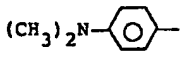
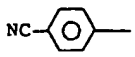
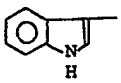
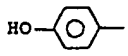
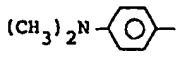
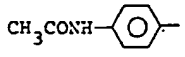
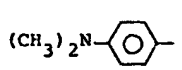
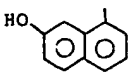
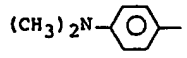
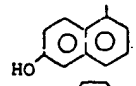
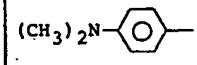
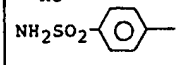
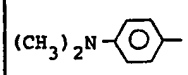
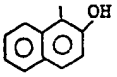
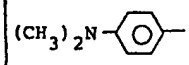
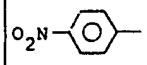
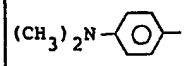
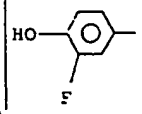
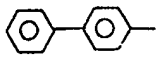
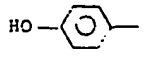
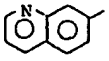
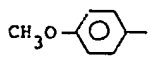
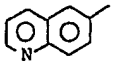
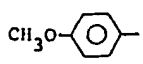
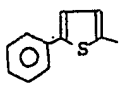
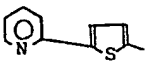
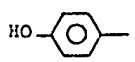
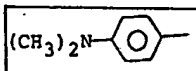
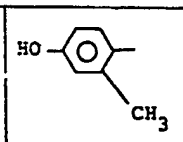
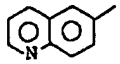
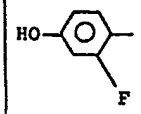
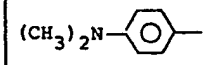
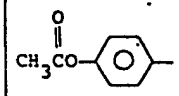
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		178 - 182	3320 (ν_{NH}), 1710, 1695, 1670
		212 - 214	1690
		140 - 143	2220 (ν_{CN}), 1685
		217 - 222	1680
		197 - 199	3300 (ν_{NH}), 1685, 163[illegible]
		192 - 194	1665
		204 - 205	1675
		180 - 185	1705, 1675
		206 - 207	1690
		134 - 136	1700, 1685
		179 - 182	1685
		180 - 184	1710
		151.5 - 152.5	1700
		157 - 158	1710
		154 - 156	1700
		220 - 223	1700

TABLE 9 (cont'd)

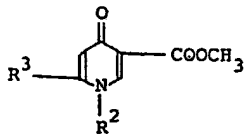
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		163 - 167	1655
		231 - 234	1695
		188 - 191	1705, 1665

(2) In 12 ml of N,N-dimethylformamide was dissolved 1.7 g of methyl 2-(4-hydroxyphenylamino-methylene)-5-(2-naphthyl)-3-oxo-4-pentenoate, and they were reacted at 140°C for 2 hours. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform/methanol (19:1 by volume) mixture). The purified oily substance was dissolved in 15 ml of dioxane and the resulting solution was heated to 80°C. To this solution was added dropwise at 80°C a solution formed by dissolving 1.1 g of 2,3,5,6-tetrachloro-p-benzoquinone in 15 ml of dioxane. After this addition was completed, the solvent was removed by distillation under reduced pressure, and to the residue was added 20 ml of a chloroform/methanol (5:1 by volume) mixed solvent. The crystals thus formed were collected by filtration, washed with 5 ml of the same mixed solvent as mentioned above, and then dried to obtain 0.75 g of methyl 1-(4-hydroxyphenyl)-6-(2-naphthyl)-4-oxo-1,4-dihydronicotinate having a melting point of 280°C or more.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1730, 1710.

The compounds shown in Table 10 were obtained in the same manner.

TABLE 10



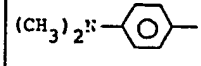
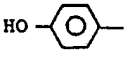
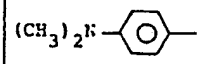
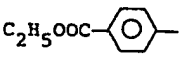
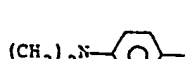
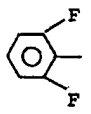
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>280	1725, 1700
		205 - 209	1740, 1720, 1700
		228 - 231	1705

TABLE 10 (cont'd)

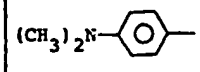
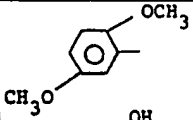
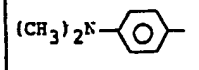
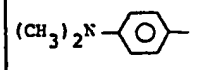
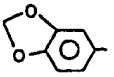
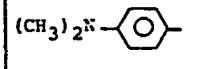
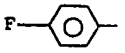
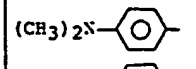
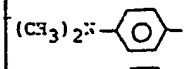
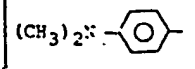
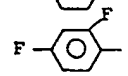
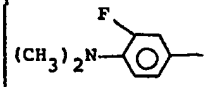
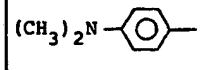
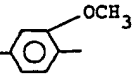
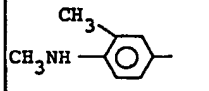
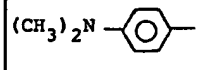
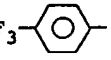
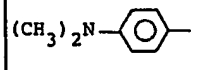
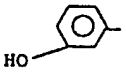
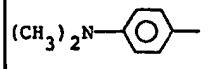
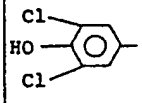
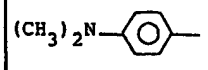
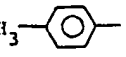
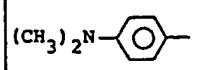
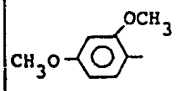
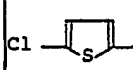
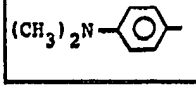
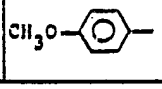
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		241 - 243	1730, 1700
		272 - 274	1730, 1700
		281.5 - 283.5	1735, 1700
		248 - 249	1730, 1720
		275 - 276	1735, 1700
		216 - 217	1730, 1700
		147 - 148	1725, 1700
		275 - 277	1730, 1710
		168 - 170	1730, 1700
		236 - 238	1730, 1700
		> 280	1735
		> 280	1725, 1705
		> 280	1730, 1700
		249 - 250	1730, 1700
		221 - 222	1725
		246 - 248	1735
		232 - 234	1735, 1700

TABLE 10 (cont'd)

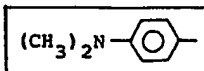
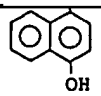
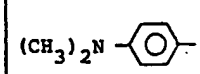
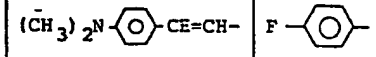
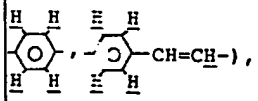
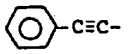
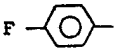
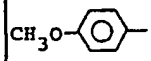
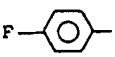
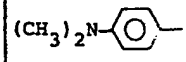
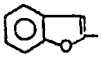
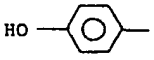
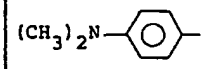
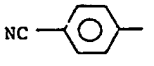
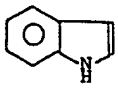
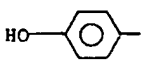
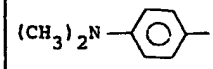
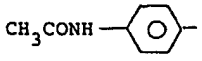
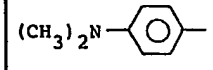
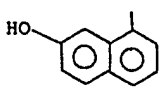
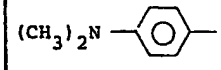
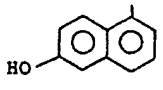
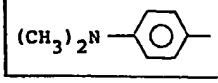
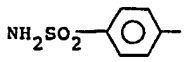
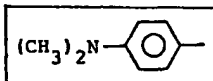
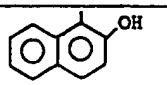
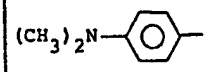
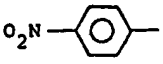
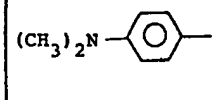
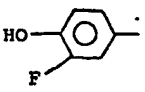
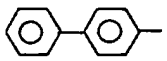
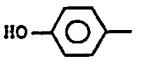
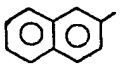
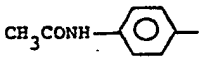
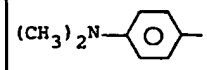
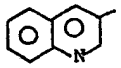
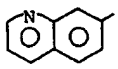
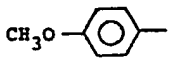
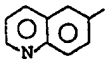
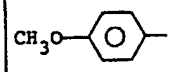
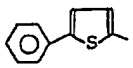
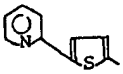
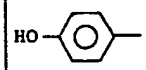
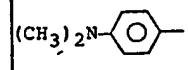
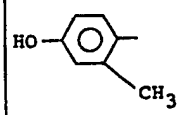
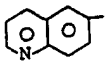
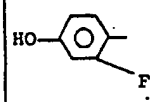
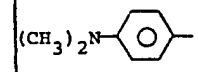
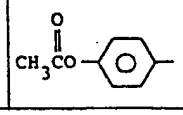
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		228 - 235	1730, 1700
		>250	1730, 1705
		NMR (d_6-DMSO) δ values: 2.95 (6H, s, $-N(CH_3)_2$), 3.74 (3H, s, $-COOCH_3$), 6.10 (1H, d, J=16 Hz, ), 6.54 - 7.90 (9H, m, ), 6.76 (1H, s, C_5-H), 8.20 (1H, s, C_2-H)	
		156 - 160	2220 ($\nu_{C\equiv C}$), 1730
		>250	1730
		>260	1735, 1720
		>250	1690
		226 - 228	2230 (ν_{CN}), 1735, 1700
		>250	1715
		279 - 280	1715, 1685
		>280	1725, 1700
		>280	1720, 1700
		180 - 181	1730, 1700

TABLE 10 (cont'd)

R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		198 - 206	1725, 1700
		213 - 217	1730, 1700
		>280	1725, 1700
		>280	1725, 1700
		167 - 170	1725, 1680
		>280	1735, 1700
		263 - 265	1735, 1705
		205.5 - 206.5	1730, 1700
		233 - 235	1730, 1700
		>250	1700
		246 - 248	1730, 1700
		>250	1730, 1710
		236 - 238	1730, 1680

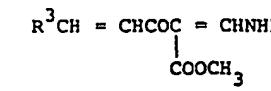
Example 3

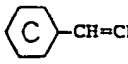
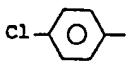
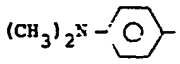
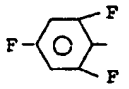
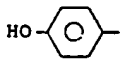
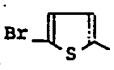
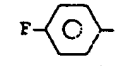
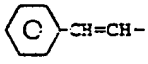
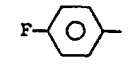
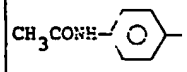
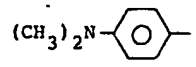
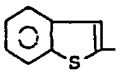
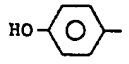
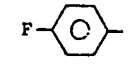
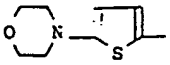
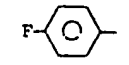
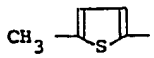
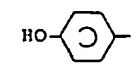
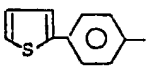
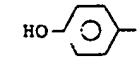
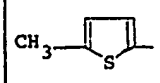
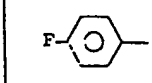
(1) To 2.5 g of methyl 5-(4-acetaminophenyl)-3-oxo-4-pentenoate were added 2.0 g of acetic anhydride and 1.4 g of ethyl orthoformate, and they were reacted at 80°C for one hour. The resulting ethyl acetate was removed by distillation under reduced pressure, and the residue was dissolved in 15 ml of benzene, and to the resulting solution was added 1.1 g of p-fluoroaniline and they were reacted at room temperature for one hour. After completion of the reaction, the precipitated crystals were collected by filtration, washed with 10 ml of benzene and then dried to obtain 2.9 g of methyl 2-(4-fluorophenylaminomethylene)-5-(4-acetaminophenyl)-3-oxo-4-pentenoate having a melting point of 161 – 164°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1705, 1660.

The compounds shown in Table 11 were obtained in the same manner.

TABLE 11



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		180 - 181	1700
		161 - 163	1705
		-	1725, 1700
		155 - 157	1703
		178 - 179.5	1690
		-	3300 (ν_{NH}) 1690, 1660 [neat]
		180 - 182	1625
		204 - 206	1703
		153 - 156	1690
		197 - 199	1700
		183 - 186	1700
		122 - 125	1690

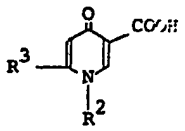
(2) In 25 ml of N,N-dimethylformamide was dissolved 2.9 g of methyl 2-(4-fluorophenylaminomethylene)-5-(4-acetaminophenyl)-3-oxo-4-pentenoate, and they were reacted at 140°C for 2 hours. After completion of the reaction, the solvent was removed by distillation under reduced pressure and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform) to obtain an oily substance. This oily sugstance was dissolved in 30 ml of benzene, followed by dropwise addition thereto of a solution of 2.06 g of 2,3,5,6-tetrachloro-p-benzoquinone in 18 ml of benzene at 80°C. After completion of this dropwise addition,

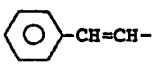
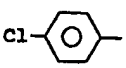
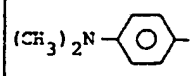
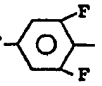
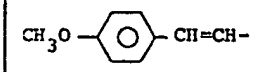
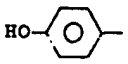
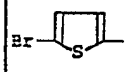
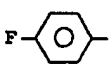
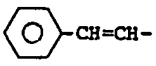
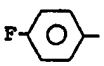
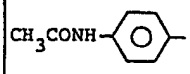
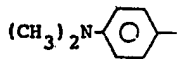
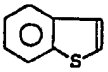
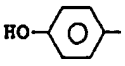
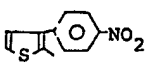
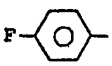
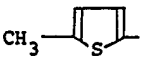
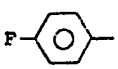
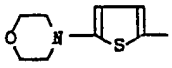
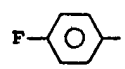
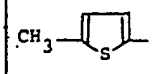
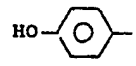
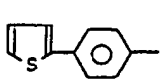
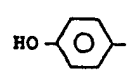
the reaction mixture was cooled to room temperature, and the precipitated crystals were collected by filtration and washed with 30 ml of benzene. These crystals were then dissolved in a mixed solution of 20 ml of methanol and 20 ml of a 1 N aqueous sodium hydroxide solution, and they were reacted at room temperature for 30 minutes. The reaction solution was adjusted to a pH of 6.0 with acetic acid and the precipitated crystals were collected by filtration, washed with water and dried to obtain 2.3 g of 6-(4-acetaminophenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 249 - 250°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720.

The compounds shown in Table 12 were obtained in the same manner.

Table 12



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		240 - 242	1725, 1710
		218 - 221	1730
		-	1720, 1700
		204 - 206	1700
		>250	1725, 1705
		165 - 168	1730, 1685
		>250	1720
		>250	1720
		182 - 184	1715
		>250	1720, 1710
		>250	1715
		>250	1720

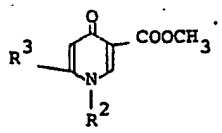
Example 4

In 10 ml of N,N-dimethylformamide was dissolved 2.0 g of methyl 5-(3-methyl-4-dimethylaminophenyl)-3-oxo-4-pentenoate, and 1.1 g of N,N-dimethylformamidodimethylacetal was added to the resulting solution, after which they were reacted at 70°C for 1.5 hours. To the reaction mixture was then added 1.0 g of p-fluoroaniline at 70°C, and they were reacted at 80°C for 2 hours and further at 140°C for 3 hours. After completion of the reaction, the reaction mixture was cooled to room temperature and the solvent was removed by distillation under reduced pressure. The residue was purified by a column chromatography (Wako Silico Gel C-200; eluent: chloroform) to obtain an oily substance. This oily substance was dissolved in 30 ml of dioxane, and to this solution was added dropwise a solution of 2.1 g of 2,3-dichloro-5,6-dicyano-p-benzoquinone in 10 ml of benzene at 80°C. Thereafter, the mixture was subjected to reaction at the same temperature for 30 minutes and the solvent was removed by distillation under reduced pressure. The residue was suspended in 50 ml of chloroform and 50 ml of water, and after adjusting this suspension to a pH 7.5 with sodium hydrogencarbonate, the organic layer was separated, washed successively with 10 ml of water and 20 ml of a saturated aqueous solution of sodium chloride and then dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain 1.8 g of methyl 1-(4-fluorophenyl)-6-(3-methyl-4-dimethylaminophenyl)-4-oxo-1,4-dihydronicotinate having a melting point of 217-220°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1725, 1705.

The compounds shown in Table 13 were obtained in the same manner.

TABLE 13



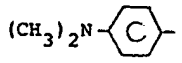
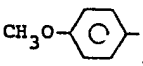
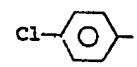
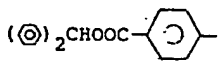
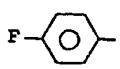
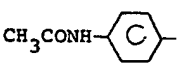
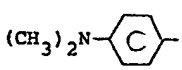
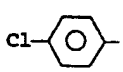
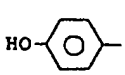
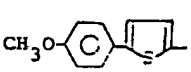
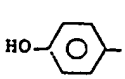
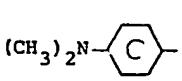
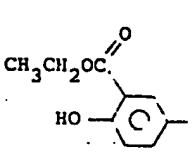
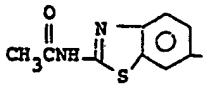
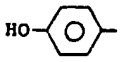
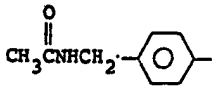
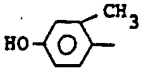
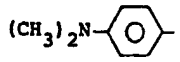
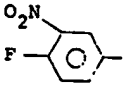
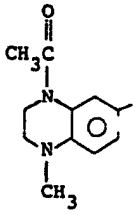
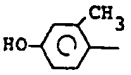
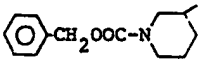
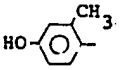
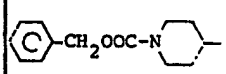
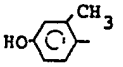
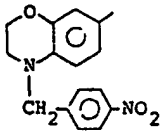
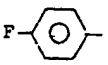
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>260	1735, 1720
		>250	1730
		195 - 197	1720, 1700
		167 - 171	1730, 1680
		156 - 166	1710, 1685
		>250	1690
		>250	1705
		251 - 254	1720, 1700
		126 - 129	1735, 1695, 1675

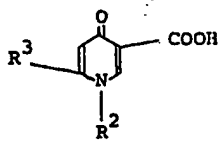
TABLE 13 (cont'd)

R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>250	1720, 1690
		266 - 268	1725
		>250	1735, 1700
		>250	1730, 1700
		136 - 137.5	1730, 1710, 1695
		125 - 127	1735, 1705, 1695
		-	1725, 1700

Example 5

(1) In the same manner as in Example 1-(4), the corresponding methyl esters were hydrolyzed to obtain the compounds shown in Table 14.

TABLE 14



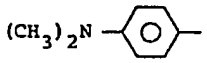
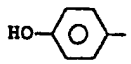
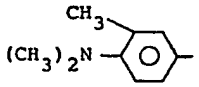
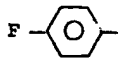
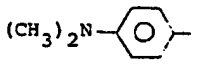
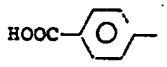
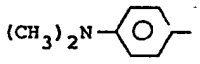
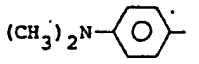
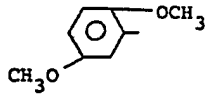
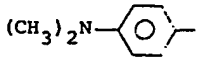
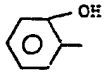
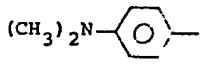
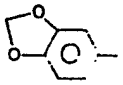
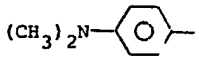
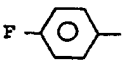
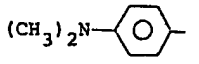
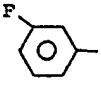
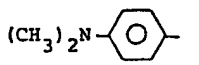
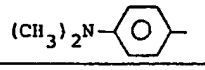
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>280	1725, 1700
		212 - 214	1720, 1700
		228.5 - 231	1710, 1690
		230 - 231	1720, 1700
		238 - 240	1720, 1700
		>280	1725, 1705
		226 - 228	1720, 1700
		230 - 231	1720, 1700
		243 - 245	1720, 1700
		217 - 218	1720, 1700
		197 - 199	1725, 1700

TABLE 14 (cont'd)

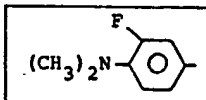
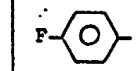
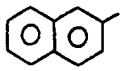
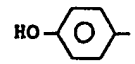
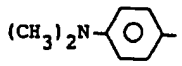
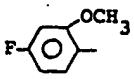
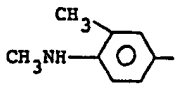
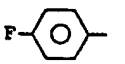
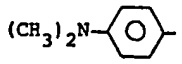
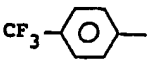
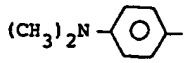
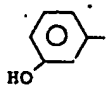
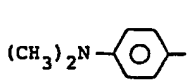
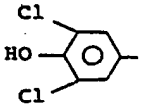
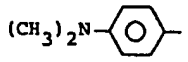
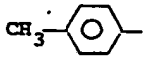
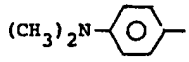
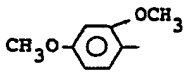
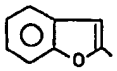
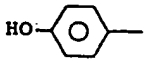
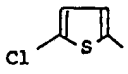
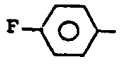
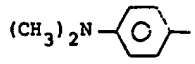
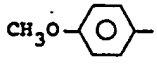
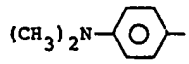
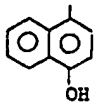
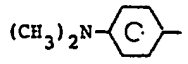
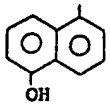
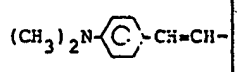
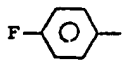
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		255 - 257	1720, 1705
		>260	1745, 1715
		192 - 195	1725, 1700
		166 - 167	3420 (ν_{NH}), 1725, 1705
		180 - 182	1725, 1700
		252 - 255	1725, 1705
		>290	1725, 1705
		201 - 203	1715
		181 - 185.5	1720, 1700
		>250	1730
		169 - 171	1725, 1700
		224 - 225	1715
		>250	1730, 1710
		>250	1725
		>230	1725, 1705

TABLE 14 (cont'd)

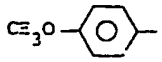
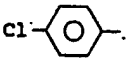
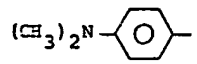
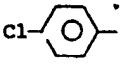
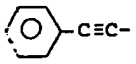
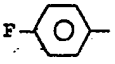
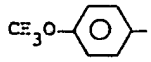
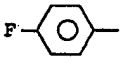
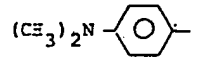
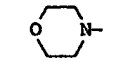
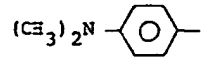
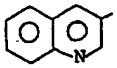
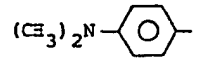
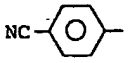
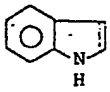
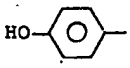
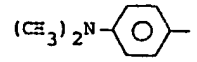
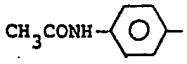
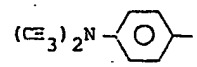
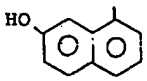
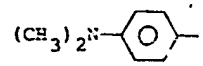
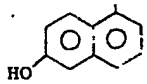
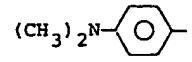
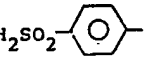
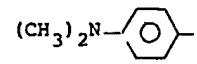
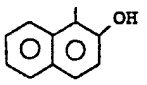
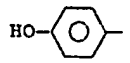
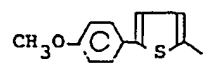
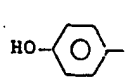
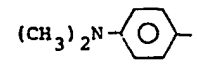
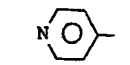
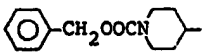
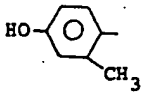
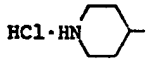
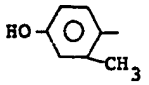
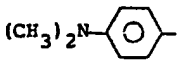
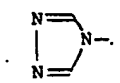
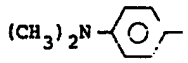
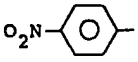
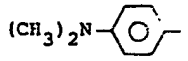
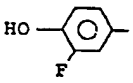
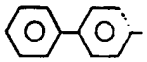
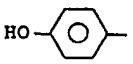
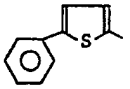
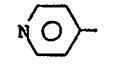
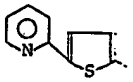
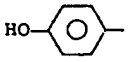
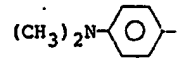
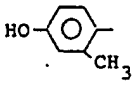
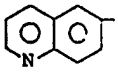
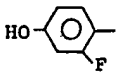
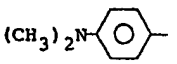
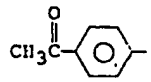
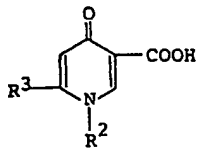
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>260	1710
		223 - 225	1705
		242 - 246	2220 ($\nu_{C\equiv C}$), 1710
		202 - 203	1695
		>260	1725, 1700
		207 - 209	1720, 1700
		273 - 275	2225 (ν_{CN}), 1725, 1700
		196 - 201	1710
		272 - 273	3270 (ν_{CN}), 1720, 1705, 1685
		180 - 182	1725, 1700
		>280	1725, 1710
		255 - 257	1720, 1700
		>250	1710
		274 - 276	3250 (ν_{OH}), 1740
		>250	1750
		>260	1710

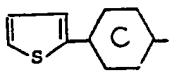
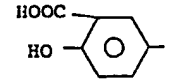
TABLE 14 (cont'd)

R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		123 - 129	1730, 1710, 1690
		242 - 250	1720
		>280	1690
		>280	1725, 1710
		>280	1730, 1700
		>280	1730, 1700
		>250	1720, 1700
		>250	1705
		>280	1725, 1700
		196 - 198	1715, 1700
		253 - 255	1720, 1680

(2) Methyl 1-[4-(3-ethyloxycarbonyl-4-hydroxy)phenyl]-6-[4-(thiophen-2-yl)phenyl]-4-oxo-1,4-dihydronicotinate was hydrolyzed in the same manner as in Example 1-(4) to obtain the compound shown in Table 15.

TABLE 15



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>280	1725, 1710

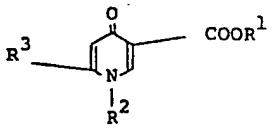
Example 6

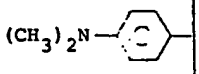
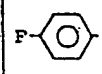
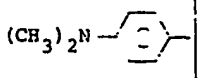
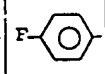
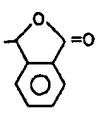
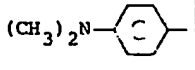
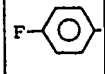
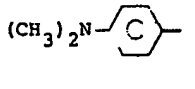
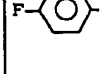
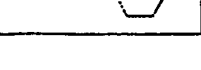
In 10 ml of chloroform was dissolved 1 g of 1-(4-fluorophenyl)-6-(4-dimethylaminophenyl)-4-oxo-1,4-dihydronicotinic acid, and to the resulting solution were then added 0.32 g of triethylamine and 0.76 g of pivaloyloxyethyl iodide at room temperature, after which the resulting mixture was subjected to reaction at the same temperature for 2 hours. After completion of the reaction, the reaction mixture was washed successively with 20 ml of a 0.1 N aqueous sodium hydroxide solution and 20 ml of water and dried with anhydrous magnesium sulfate. Then, the solvent was removed by distillation under reduced pressure, and to the residue was added 20 ml diethyl ether/n-hexane (1:1 by volume) mixed solvent, after which insolubles were removed by filtration to obtain 0.6 g of 1-pivaloyloxyethyl 1-(4-fluorophenyl)-6-(4-dimethylamino-phenyl)-4-oxo-1,4-dihydronicotinate having a melting point of 117-120°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1745, 1720.

The compounds shown in Table 16 were obtained in the same manner.

TABLE 16



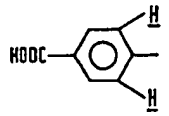
R^3	R^2	R^1	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		$-CH_2CH_2N(CH_3)_2$	186 - 188	1725, 1700
			220 - 223	1785, 1730, 1700
		$-CH_2CH_2CH_2CH_3$	170 - 174	1730, 1695
		$-CH_2CH_2CH_3$	181 - 183	1720, 1700
		$-CH_2CH_3$	222 - 225	1725, 1695

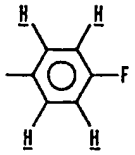
Example 7

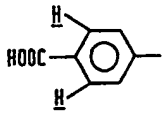
In a mixed solvent of 2.5 ml of anisole and 2.5 ml of trifluoroacetic acid was dissolved 0.25 g of methyl 6-(4-diphenylmethyloxycarbonylphenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinate, and they were reacted at room temperature for 1.5 hours. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and the residue was dissolved in a mixed solvent of 2.5 ml of ethanol and 2.5 ml of a 1 N aqueous sodium hydroxide solution, and the resulting solution was subjected to reaction at room temperature for 3 hours. After completion of the reaction, 20 ml of water and 20 ml of benzene were added to the reaction mixture and the aqueous layer was separated. The aqueous solution thus obtained was adjusted to a pH of 5.5 with acetic acid and the precipitated crystals were collected by filtration, to obtain 0.10 g of 6-(4-carboxyphenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 280°C or more.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720, 1710

NMR (d_6-DMSO) δ value:

6.97 (1H, s, C_5–H), 7.34 (2H, d, J=8Hz, ),

7.16-7.79 (4H, m,  , 7.94 (2H, d, J=8Hz,

), 8.73 (1H, s, C_2–H)

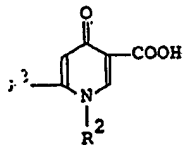
Example 8

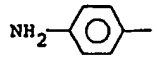
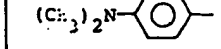
In a mixed solvent of 3 ml of methanol and 3 ml of 10% by weight aqueous sodium hydroxide solution was dissolved 0.5 g of 6-(4-actaminophenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinic acid, and the resulting solution was subjected to reaction at 60°C for 4 hours. After completion of the reaction, the reaction mixture was cooled to room temperature and adjusted to a pH of 6.0 with acetic acid. The precipitated crystals were collected by filtration, washed with water and dried to obtain 0.36 g of 6-(4-aminophenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 262 - 266°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1715.

A corresponding acetamino form was hydrolyzed in the same manner, to obtain the compound shown in Table 17.

TABLE 17



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		265 (decomp.)	1710

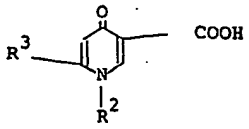
Example 9

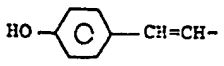
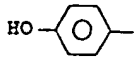
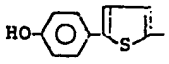
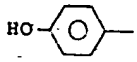
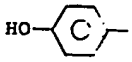
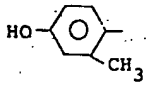
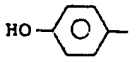
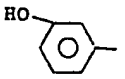
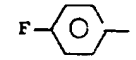
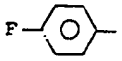
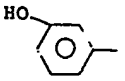
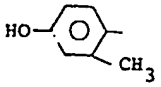
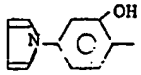
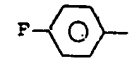
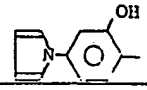
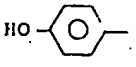
In 7 ml of 47% by weight hydrobromic acid was suspended 0.2 g of 1-(4-fluorophenyl)-6-(4-methoxyphenyl)-4-oxo-1,4-dihydronicotinic acid was suspended, and the suspension was refluxed for 2 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with 10 ml of water, adjusted to a pH of 12 with a 20% by weight aqueous sodium hydroxide solution, and washed with 20 ml of chloroform. This aqueous solution was then adjusted to a pH of 6.0 with acetic acid and the precipitated crystals were collected by filtration, and washed with water to obtain 0.15 g of 1-(4-fluorophenyl)-6-(4-hydroxyphenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 185 - 193°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1705.

The compounds shown in Table 18 were obtained in the same manner.

TABLE 18



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>200	1730, 1705
		>250	1700
		>250	1720, 1705
		270 - 271	1720
		>250	1720, 1700
		144 - 145	1720
		157 - 160	1715
		173 - 175	1730
		>250	1710, 1700

Example 10

In 10 ml of ethanol were suspended 0.3 g of 6-(4-aminophenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinic acid and 0.15 g of 5-nitrofurfural, and the suspension was subjected to reaction at 80°C for 2 hours. After completion of the reaction, the reaction mixture was cooled to room temperature and the insolubles were removed by filtration. The solvent was removed by distillation under reduced pressure. Then, 10 ml of diethyl ether was added to the residue, and the insolubles were collected by filtration to obtain 0.13 g of 1-(4-fluorophenyl)-6-[4-{(5-nitrofurfurylidene)amino}-phenyl]-4-oxo-1,4-dihydronicotinic acid having a melting point of 129-131°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720, ν_{NO_2} 1350

Example 11

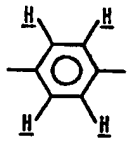
In 50 ml of methanol was suspended 6.5 g of 6-(4-aminophenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinic acid, and the suspension was cooled to 5°C, after which 3.9 g of thionyl chloride was added dropwise thereto over 10 minutes. After completion of the dropwise addition, the resulting mixture was refluxed for 6 hours, and then cooled to room temperature, after which the solvent was removed by distillation under reduced pressure. To the residue were added 30 ml of water and 30 ml of chloroform, and the resulting mixture was adjusted to a pH of 7 with sodium hydrogen-carbonate, after which the aqueous layer was separated, washed with 30 ml of a saturated aqueous solution of sodium chloride, and then dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The resulting crystalline substance was washed with 50 ml of diethyl ether to obtain 6.7 g of methyl 6-(4-aminophenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinate having a melting point of 250°C or more.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720.

NMR (d-TFA) δ values:

3.75 (3H, s, $-COOCH_3$), 4.15 (2H, bs, $-NH_2$), 6.20-7.61

(9H, m,



x2, C_5-H), 8.35 (1H, s, C_2-H)

Example 12

In a mixed solvent of 5 ml of acetic acid and 4 ml of water was dissolved 0.7 g of methyl 6-(4-aminophenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinate, and to this solution was added dropwise a solution of 0.3 g of sodium cyanate in 3 ml of water at room temperature over 5 minutes, after which the mixture was subjected to reaction at the same temperature for 2 hours. After completion of the reaction, 10 ml of water was added to the reaction mixture and the precipitated crystals were collected by filtration. These crystals were suspended in a mixed solution of 5 ml of methanol and 5 ml of a 1 N aqueous sodium hydroxide solution, and the suspension was stirred at room temperature for 30 minutes. The homogenized solution was adjusted to a pH of 6.0 with acetic acid and the precipitated crystals were collected by filtration, washed with water and dried to obtain 0.5 g of 1-(4-fluorophenyl-4-oxo-6-(4-ureidophenyl)-1,4-dihydronicotinic acid having a melting point of 185 - 190°C (decomp.).

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720.

Example 13

In 5 ml of N,N-dimethylformamide was dissolved 0.35 g of methyl 6-(4-aminophenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinate, and 1 g of 2-bromoethanol and 0.3 g of triethylamine were added to the solution, after which the resulting mixture was refluxed for 2 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, and 10 ml of water was then added thereto, after which the resulting mixture was extracted with 10 ml of chloroform. The extract was washed with 10 ml of a saturated aqueous solution of sodium chloride and dried with anhydrous magnesium sulfate. Then, the solvent was removed by distillation under reduced pressure and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform) to obtain an oily substance. This oily substance was dissolved in a mixture of 2 ml of methanol and 3 ml of a 1 N aqueous sodium hydroxide solution, and they were reacted at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was adjusted to a pH of 6.0 with acetic acid, and the precipitated crystals were collected by filtration, washed with water and dried to obtain 0.15 g of 1-(4-fluorophenyl)-6-[4-N-(2-hydroxyethyl)aminophenyl]-4-oxo-1,4-dihydronicotinic acid having a melting point of 226 - 228°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720

Example 14

In 5 ml of N,N-dimethylformamide was dissolved 0.5 g of methyl 6-(4-aminophenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinate, and 0.23 g of allyl chloride and 0.3 g of triethylamine were added thereto, and the resulting mixture was refluxed for 3 hours. After completion of the reaction, the reaction mixture was cooled, and 10 ml of water was added thereto, after which the resulting mixture was extracted with 10 ml of chloroform. The extract was washed with 10 ml of a saturated aqueous solution of sodium chloride and dried with anhydrous magnesium sulfate. The solvent was then removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silico Gel C-200; eluant: chloroform) to obtain an oily substance. This oily substance was dissolved in a mixture of 2 ml of methanol and 3 ml of a 1 N aqueous sodium hydroxide solution, and they were reacted at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was adjusted to a pH of 6.0 with acetic acid, and the precipitated crystals were collected by filtration, washed with water, and dried to obtain 0.32 g of 6-(4-N-allylaminophenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 183 - 185°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720.

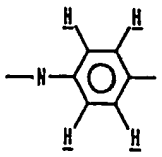
Example 15

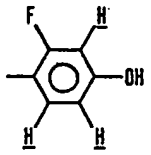
In 10 ml of 47% by weight hydrobromic acid was suspended 0.3 g of 1-(2-fluoro-4-methoxyphenyl)-6-(4-dimethylaminophenyl)-4-oxo-1,4-dihydronicotinic acid, and the suspension was refluxed for 2 hours. After completion of the reaction, the reaction mixture was cooled to room temperature and diluted with 10 ml of water. The resulting solution was then adjusted to a pH of 12 with 20% by weight aqueous sodium hydroxide solution and washed with 20 ml of chloroform. The aqueous layer was adjusted to a pH of 6.0 with acetic acid, and the precipitated crystals were collected by filtration, washed with 10 ml of water, and dried to obtain 0.17 g of 1-(2-fluoro-4-hydroxyphenyl)-6-(4-dimethylaminophenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 250°C or more.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720.

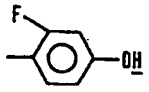
NMR (d_6-DMSO) δ values:

2.97 (6H, s, $-N(CH_3)_2$), 6.52-7.35 (8H, m,



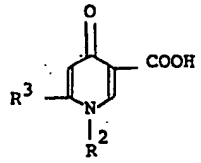


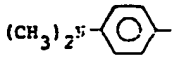
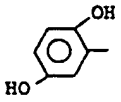
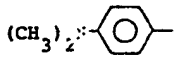
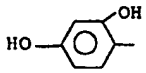
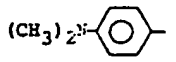
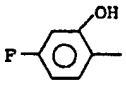
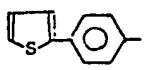
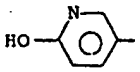
C_5-H), 8.60 (1H, s, C_2-H), 10.45 (1H, bs,



The compounds shown in Table 19 were obtained in the same manner.

TABLE 19



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		251 - 254	1720, 1700
		>280	1710
		>280	1720
		>250	1720

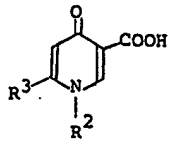
Example 16

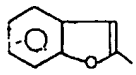
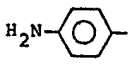
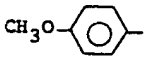
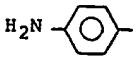
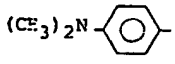
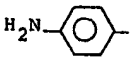
In a mixed solvent of 10 ml of ethanol and 10 ml of a 10% by weight aqueous sodium hydroxide solution was dissolved 0.5 g of methyl 1-(4-acetaminophenyl)-6-(2-naphthyl)-4-oxo-1,4-dihydronicotinate, and the solution was refluxed for 3 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, and diluted with 20 ml of water. This solution was then adjusted to a pH of 5.5 acetic acid, and the precipitated crystals were collected by filtration, washed with water, and dried to obtain 0.38 g of 1-(4-aminophenyl)-6-(2-naphthyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 148 - 151°C.

IR (KBr) cm^{-1}: ν_{NH} 3470, 3360.
$\nu_{C=O}$ 1715, 1700.

The compounds shown in Table 20 were obtained in the same manner.

TABLE 20



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>250	1720, 1700
		237 - 239	1720, 1700
		147 - 151	1710, 1700

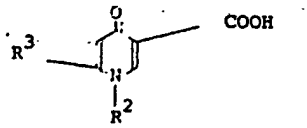
Example 17

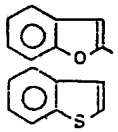
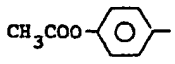
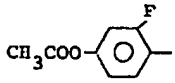
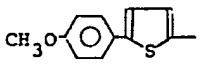
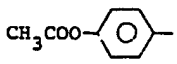
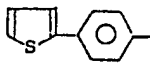
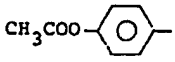
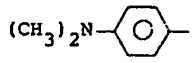
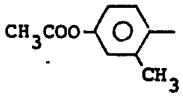
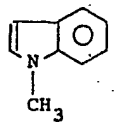
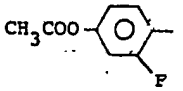
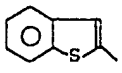
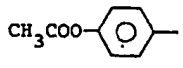
With 1 g of 6-(4-dimethylaminophenyl)-1-(4-hydroxyphenyl)-4-oxo-1,4-dihydronicotinic acid was mixed 10 ml of acetic anhydride and the resulting mixture was subjected to reaction at 103°C for 2 hours. After completion of the reaction, the reaction mixture was cooled to room temperature and introduced into 150 ml of water. After stirring the mixture for 1 hour, 150 ml of ethyl acetate was added to the mixture, and the organic layer was separated, washed with 100 ml of water and then with 50 ml of a saturated aqueous solution of sodium chloride, and dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure, and to the residue was added 20 ml of diethyl ether, and the resulting mixture was filtered to obtain 0.75 g of 1-(4-acetyloxyphenyl)-6-(4-dimethylaminophenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 128 - 131°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1760, 1720, 1700.

The compounds shown in Table 21 were obtained in the same manner.

TABLE 21



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		231 - 234	1760, 1720
		178 - 179	1765, 1730
		235 - 237	1760, 1700
		205 - 207	1760, 1740, 1720
		194 - 195	1760, 1715
		230.5 - 233	1770, 1730
		229 - 231	1760, 1720

Example 18

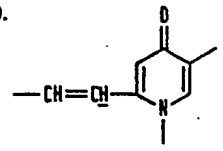
(1) In the same manner as in Example 4, methyl 1-(4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydronicotinate (m.p. 190 - 195°C) was prepared from methyl 3-oxo-4-hexenoate and 4-fluoroaniline, and 0.7 g of this ester was mixed with 0.32 g of nicotinaldehyde and 0.58 g of acetic anhydride, and they were refluxed for 5 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, and 20 ml of water was added thereto, after which the mixture was successively extracted with three 40-ml portions of chloroform. The chloroform layer was washed with 50 ml of a saturated aqueous solution of sodium chloride and dried with anhydrous magnesium sulfate, and the solvent was removed by sidtillation under reduced pressure. The residue was purified by a column chromatography (Wako Silico Gel C-200; eluant: chloroform) to obtain 0.496 g of methyl 1-(4-fluorophenyl)-6-[2-(pyridin-3-yl)ethenyl]-4-oxo-1,4-dihydronicotinate having a melting point of 201 - 204°C.

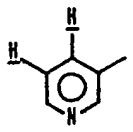
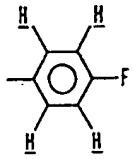
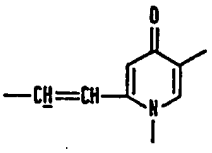
IR (KBr) cm^{-1}: $\nu_{C=O}$ 1725, 1700

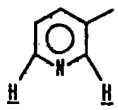
(2) In a mixture of 9 ml of ethanol and 9 ml of a 10% by weight aqueous sodium hydroxide solution was suspended 0.45 g of methyl 1-(4-fluorophenyl)-6-[2-(pyridin-3-yl)ethenyl]-4-oxo-1,4-dihydronicotinate and the suspension was subjected to reaction at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was adjusted to a pH of 6.0 with acetic acid, and the precipitated crystals were collected by filtration and dried to obtain 0.357 g of 1-(4-fluorophenyl)-6-[2-(pyridin-3-yl)ethenyl]-4-oxo-1,4-dihydronicotinic acid having a melting point of 250°C or more.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1710.

NMR (d_6-DMSO) δ values:

6.64 (1H, d, J=16Hz, ), 7.10-8.00

(8H, m,  ,  , C_5–H, ),

8.50-8.85 (3H, m,  , C_2–H)

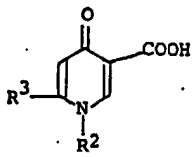
Example 19

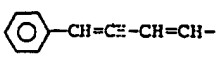
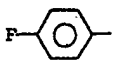
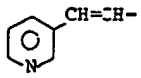
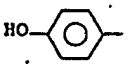
To 0.7 g of 1-(4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydronicotinic acid was added 0.33 g of isonicotinaldehyde and 0.61 g of acetic anhydride, and they were refluxed for 5 hours. After completion of the reaction, 30 ml of water was added to the reaction mixture, and the mixture was successively extracted with 30-ml portions of chloroform. The chloroform layer was separated, washed with 20 ml of a saturated aqueous solution of sodium chloride, and then dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain 0.42 g of 1-(4-fluorophenyl)-6-[2-(pyridin-4-yl)ethenyl]-4-oxo-1,4-dihydronicotinic acid having a melting point of 205 - 215°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1715, 1690

The compounds shown in Table 22 were obtained in the same manner.

TABLE 22



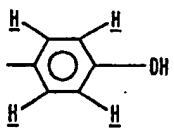
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		213 - 215	1720
		218 - 224	1700

Example 20

In 5 ml of benzene was dissolved 1 g of methyl 3-oxo-5-(pyrrol-2-yl)-4-pentenoate and to this solution was added 0.74 g of N,N-dimethylformamidodimethylacetal. They were reacted at 70°C for 1.5 hours. To the reaction mixture was then added 0.56 g of 4-hydroxyaniline, and they were further reacted at room temperature for 1 hour. The precipitated crystals were collected by filtration and dissolved in 10 ml of N,N-dimethylformamide. They were reacted at 140°C for 3 hours. After completion of the reaction, the reaction mixture was cooled to room temperature and the solvent was removed by distillation under reduced pressure. The residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform) to obtain an oily substance. This oily substance was dissolved in 10 ml of dioxane, and to this solution was added dropwise a solution of 0.54 g of 2,3,5,6-tetrachloro-p-benzoquinone in 5 ml of dioxane at 95°C. Thereafter, the mixture was subjected to reaction at the same temperature for 30 minutes, and the reaction mixture was cooled to room temperature. The precipitated crystals were collected by filtration, dissolved in a mixture of 5 ml of methanol and 10 ml of a 10% by weight aqueous sodium hydroxide solution, and they were reacted at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was adjusted to a pH of 6.0 with acetic acid, and the precipitated crystals were collected by filtration, washed with water, and dried to obtain 0.3 g of 1-(4-hydroxyphenyl)-4-oxo-6-(pyrrol-2-yl)-1,4-dihydronicotinic acid having a melting point of 250°C or more.

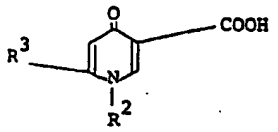
IR (KBr) cm^{-1}: $\nu_{C=O}$ 1710.

NMR (d-TFA) δ values:

7.18-7.90 (8H, m,  ,  , C_5–H), 9.0 (1H, s, C_2–H)

The compounds shown in Table 23 were obtained in the same manner.

TABLE 23



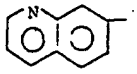
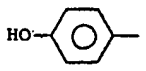
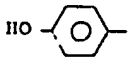
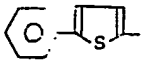
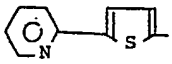
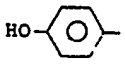
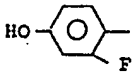
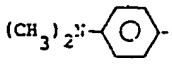
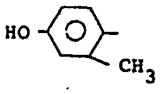
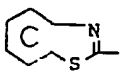
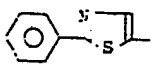
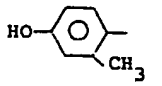
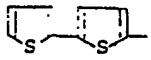
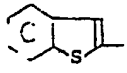
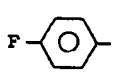
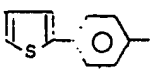
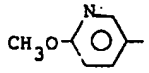
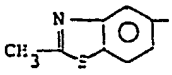
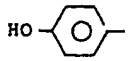
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		202 - 203.5	1720, 1700
		194 - 197	1715, 1700
		>250	1720
		>250	1705
		196 - 198	1715, 1700
		>280	1725, 1700
		>250	1730
		>250	1720
		>250	1750
		218 - 220	1715, 1700
		212 - 214	1725
		>250	1725, 1710

TABLE 23 (cont'd)

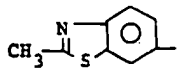
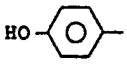
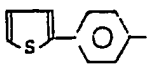
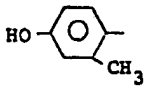
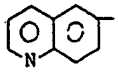
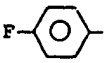
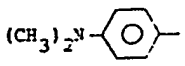
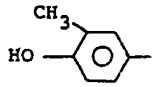
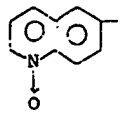
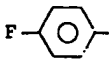
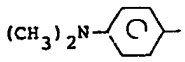
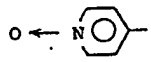
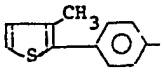
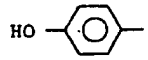
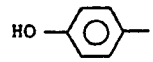
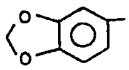
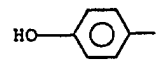
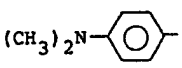
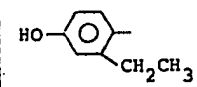
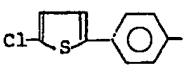
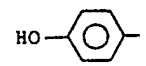
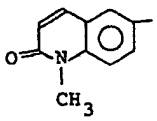
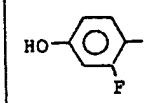
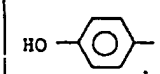
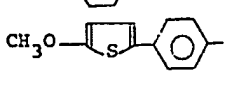
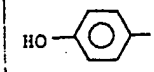
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>250	1720, 1700
		173 - 176	1715
		125 - 126	1725
		267 - 269	1730, 1700
		>250	1725, 1700
		>250	1730
		>250	1730
		>280	1720, 1705
		160 - 165	1720
		277 - 278	1725, 1700
		178 - 180	1720
		208 - 209	1725
		>250	1735
		>250	1740

TABLE 23 (cont'd)

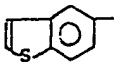
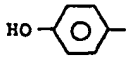
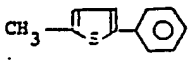
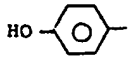
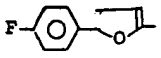
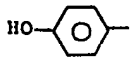
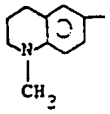
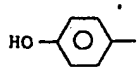
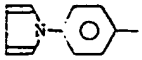
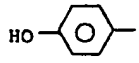
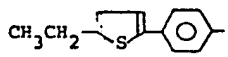
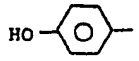
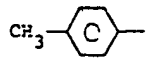
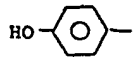
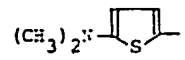
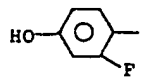
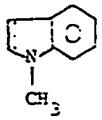
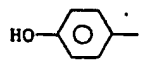
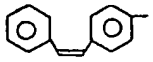
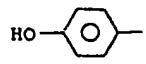
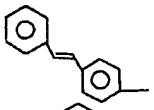
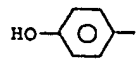
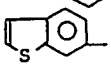
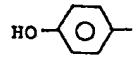
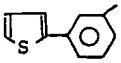
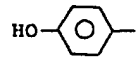
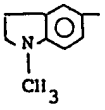
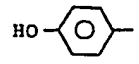
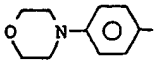
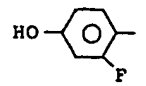
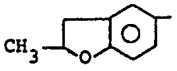
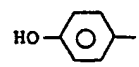
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>250	1750
		>280	1745, 1715
		>280	1725, 1715
		>250	1730
		>250	1735
		268 - 271	1735, 1700
		282 - 288	1730
		250 (decomp.)	1725
		279 - 282	1720
		>280	1730, 1710
		285 - 288	1735, 1720
		>250	1750
		>250	1730
		253 - 255.5	1730
		295 - 296	1725
		261 - 263	1720, 1700

TABLE 23 (cont'd)

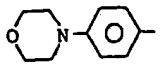
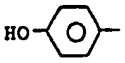
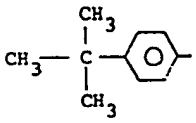
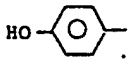
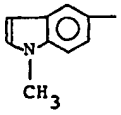
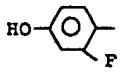
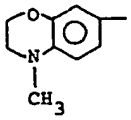
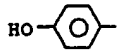
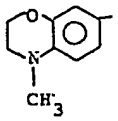
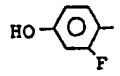
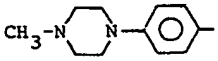
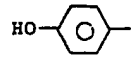
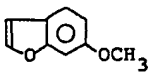
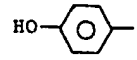
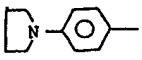
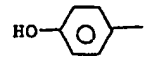
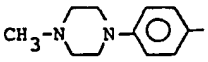
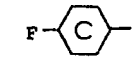
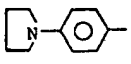
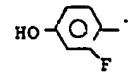
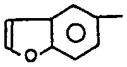
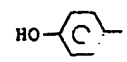
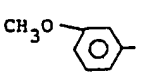
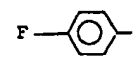
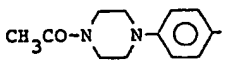
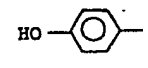
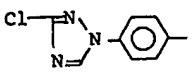
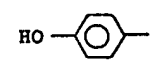
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>250	1720
		220 - 221	1730
		278 - 282	1725, 1715
		>250	1720
		>250	1720
		>250	1720
		245 - 250	1720, 1705
		>250	1710, 1690
		>250	1720
		185 - 187	1720
		281 - 283	1735
		220 - 223	1715
		195 - 197	1720, 1700, 1660
		182 - 183	1715

TABLE 23 (cont'd)

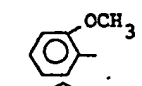
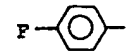
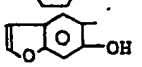
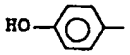
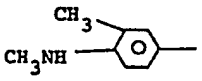
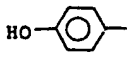
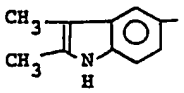
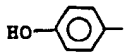
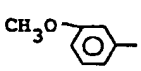
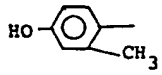
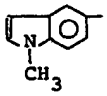
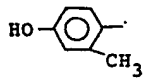
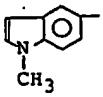
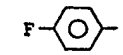
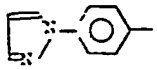
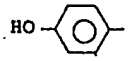
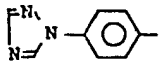
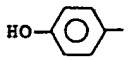
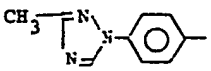
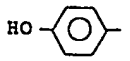
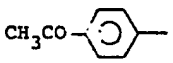
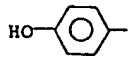
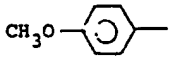
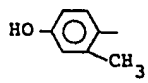
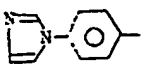
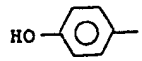
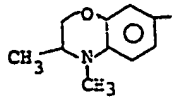
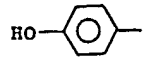
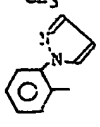
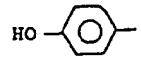
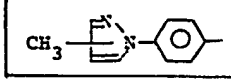
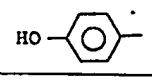
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		181 - 183	1720
		207 - 210	1705
		>250	1730
		>270	1725
		122 - 125	1720, 1700
		>250	1725, 1710
		215 - 217	1725, 1705
		172 - 174	1720
		257 - 258	1715
		>280	1710
		>280	1725, 1665
		239 - 241	1720, 1700
		220 - 223	1725
		>250	1725
		>250	1715, 1705
		>250	1720, 1710

TABLE 23 (cont'd)

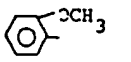
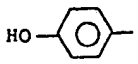
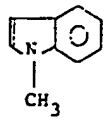
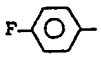
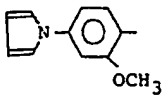
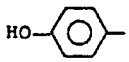
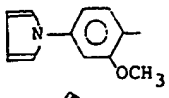
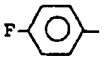
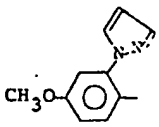
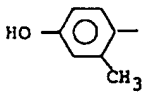
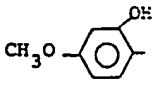
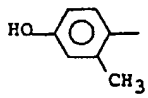
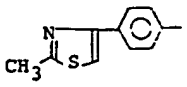
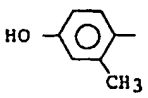
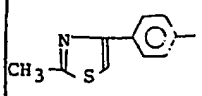
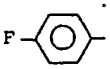
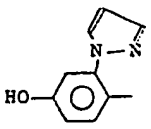
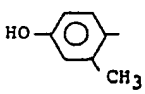
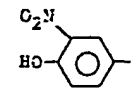
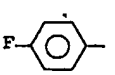
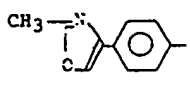
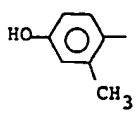
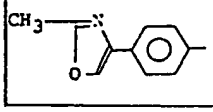
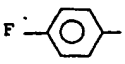
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>290	1725, 1710
		215 - 217	1725, 1705
		>250	1720, 1700
		130 - 133	1720
		168 - 171	1720
		>250	1720, 1700
		247 - 250	1720, 1710
		252 - 253	1715
		193 - 195	1720
		242 - 245	1720, 1710
		226 - 230	1710
		208 - 211	1720

TABLE 23 (cont'd)

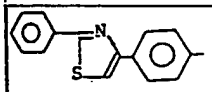
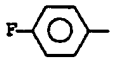
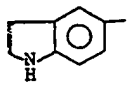
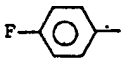
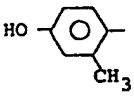
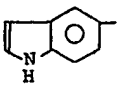
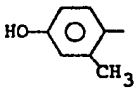
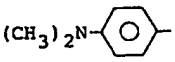
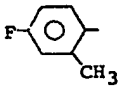
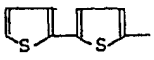
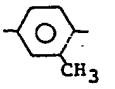
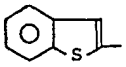
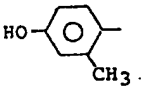
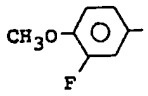
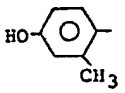
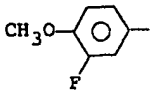
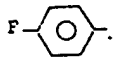
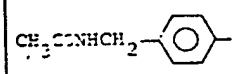
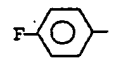
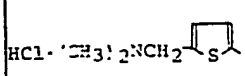
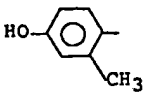
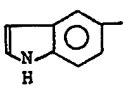
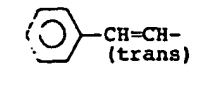
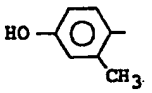
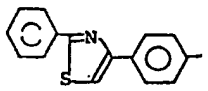
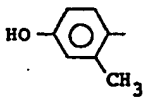
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		227 - 229	1725
		166 - 167	1730
		144 - 147	1715
		205 - 209	1715
		249 - 251	1730
		178 - 180	1720
		234 - 238	1670
		231 - 233	1730, 1710
		220 - 222	1730, 1710
		247 - 248	1720
		140 - 155	1725, 1710, 1685
		>250	1730

TABLE 23 (cont'd)

		>250	1725, 1715
		281 - 288	1720, 1700, 1680

Example 21

In 10 ml of 47% by weight hydrobromic acid was suspended 0.15 g of 1-(3,4-methylenedioxyphenyl)-6-(4-dimethylaminophenyl)-4-oxo-1,4-dihydronicotinic acid, and they were refluxed for 2 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, and diluted with 10 ml of water. This solution was adjusted to a pH of 12 with a 20% by weight aqueous sodium hydroxide solution, washed with 20 ml of chloroform, and again adjusted to a pH of 6.0 with acetic acid. This solution was extracted with 50 ml of chloroform, and the extract was washed with 30 ml of a saturated aqueous solution of sodium chloride and dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform/methanol (15:1 by volume) mixture) to obtain 0.05 g of 1-(3,4-dihydroxyphenyl)-6-(4-dimethylaminophenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 223 - 227°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720, 1700.

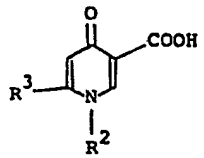
Example 22

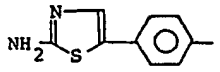
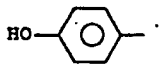
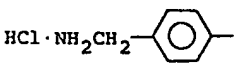
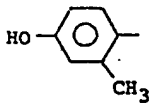
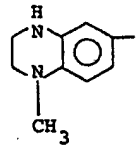
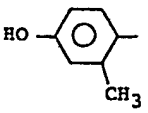
In 3 ml of methanol and 5 ml of 10% by weight aqueous sodium hydroxide solution was dissolved 0.5 g of methyl 6-(4-acetaminophenyl)-1-(3-pyridyl)-4-oxo-1,4-dihydronicotinate, and they were reacted at 60° for 4 hours. After completion of the reaction, the reaction mixture was cooled to room temperature and adjusted to a pH of 6.0 with acetic acid, and the precipitated crystals were collected by filtration, washed with 10 ml of water, and then dried to obtain 0.34 g of 6-(4-aminophenyl)-1-(3-pyridyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 207 - 208°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720, 1700.

The compounds shown in Table 24 were obtained in the same manner.

TABLE 24



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		243 - 250	1720, 1710
		>280	1720, 1700 1680
		>250	1710

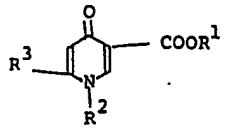
Example 23

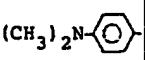
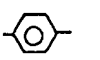
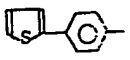
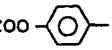
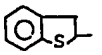
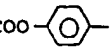
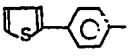
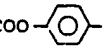
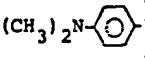
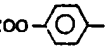
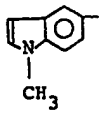
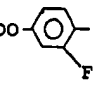
In 18 ml of anhydrous methylene chloride was dissolved 0.36 g of 1-(4-acetoxyphenyl)-6-(2-benzo[b]thienyl)-4-oxo-1,4-dihydronicotinic acid, and to this solution was added 0.137 ml of triethylamine at room temperature. The reaction mixture thus obtained was cooled to −40°C, and 0.094 ml of ethyl chlorocarbonate was added thereto. The resulting mixture was subjected to reaction at the same temperature for 1 hour. This reaction mixture was then mixed with 0.14 g of 5-indanol. The mixture was subjected to reaction for 1 hour, and elevated to room temperature. After completion of the reaction, the reaction mixture was washed successively with 15 ml of water and a saturated aqueous solution of sodium chloride, and then dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform) to obtain 0.25 g of indanyl 1-(4-acetoxyphenyl)-6-(2-benzo[b]thienyl)-4-oxo-1,4-dihydronicotinate having a melting point of 234 - 236°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1760(Sh), 1745, 1710.

The compounds shown in Table 25 were obtained in the same manner.

TABLE 25



R^3	R^2	R^1	m.p. (°C)	IR(KBr) cm^{-1}: $\nu_{C=O}$
			234 - 235	1745, 1710
			209 - 211	1760, 1745
		$-CH_2CH_3$	232 - 234	1760, 1725, 1705
		$-CH_2CH_3$	188 - 190	1765, 1730, 1690
		$-CH_2CH_2N(CH_3)_2$	186 - 190	1760, 1730, 1695
		$-CH_2CH_2N(CH_3)_2$	120 - 123	1765, 1730

Example 24

(1) In 15 ml of N,N-dimethylformamide was dissolved 0.4 g of 6-(4-dimethylaminophenyl)-1-(4-hydroxyphenyl)-4-oxo-1,4-dihydronicotinic acid at room temperature, and to this solution was added 0.33 g of potassium carbonate. The resulting mixture was heated to 100°C for 1 hour. The reaction mixture thus obtained was cooled to room temperature, and 0.2 g of methoxymethyl chloride was added thereto. The resulting mixture was subjected to reaction at room temperature for 1 hour. After completion of this reaction, the solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform/ethanol (30:1 by volume) mixture to obtain 0.16 g of methoxymethyl 6-(4-dimethylaminophenyl)-1-(4-methoxymethyloxyphenyl)-4-oxo-1,4-dihydronicotinate having a melting point of 199 - 201°C and 0.13 g of methoxymethyl 6-(4-dimethylaminophenyl)-1-(4-hydroxyphenyl)-4-oxo-1,4-dihydronicotinate having a melting point of 211 - 213°C.

Methoxymethyl 6-(4-dimethylaminophenyl)-1-(4-methoxymethyloxyphenyl)-4-oxo-1,4-dihydronicotinate:

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1725, 1695.

Methoxymethyl 6-(4-dimethylaminophenyl)-1-(4-hydroxyphenyl)-4-oxo-1,4-dihydronicotinate:

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1735, 1700.

(2) In 1 ml of ethanol was dissolved 0.08 g of methoxymethyl 6-(4-dimethylaminophenyl)-1-(4-methoxymethyloxyphenyl)-4-oxo-1,4-dihydronicotinate at room temperature, and 1 ml of a 10% by weight aqueous sodium carbonate solution was added to the resulting solution. The resulting mixture was subjected to reaction at the same temperature for 1 hour. After completion of the reaction, the reaction mixture was adjusted to a pH of 6.0 with acetic acid, and the precipitated crystals were collected by filtration, washed with

5ml of water, and dried to obtain 0.06 g of 6-(4-dimethylaminophenyl)-1-(4-methoxymethyloxyphenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 150 - 152°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720.

Example 25

In 12 ml of N,N-dimethylformamide was dissolved 0.6 g of methyl 1-(3-nitro-4-fluorophenyl)-6-(4-dimethylaminophenyl)-4-oxo-1,4-dihydronicotinate and to this solution was added 0.2 g of 5% by weight palladium carbon, and the above ester was hydrogenated under atmospheric pressure for 2 hours. Then, the catalyst was removed by filtration and the solvent was removed by distillation under reduced pressure. The resulting residue was dissolved in a mixture consisting of 2 ml of ethanol and 2 ml of a 1 N aqueous sodium hydroxide solution, and the solution was subjected to reaction at room temperature for one hour. This reaction mixture was mixed with 10 ml of water and 10 ml of chloroform, and the mixture was adjusted to a pH of 5.5 with acetic acid. The organic layer was separated, washed successively with 10 ml of water and 10 ml of a saturated aqueous solution of sodium chloride, and dried with anhydrous magnesium sulfate. Then the solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform/ethanol (100:1 by volume) mixture) to obtain 0.1 g of 1-(3-amino-4-fluorophenyl)-6-(4-dimethylaminophenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 198 - 201°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720.

Example 26

To 0.2 g of 5% by weight palladium carbon was added 5 ml of methanol, and the resulting mixture was stirred under atmospheric pressure in a hydrogen atmosphere for 10 minutes. To this mixture was added a solution prepared by dissolving 0.3 g of methyl 6-[4-(p-nitrobenzyl)-2H-3,4-dihydrobenzo-1,4-oxazin-7-yl]-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinate in 3 ml of methanol. The resulting mixture was subjected to hydrogenation at room temperature under 3 atm. for 2 hours. After completion of the reaction, the catalyst was removed by filtration and the solvent was removed by distillation under reduced pressure. The residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform/ethanol (25:1 by volume) mixture) and the fraction containing the objective substance was concentrated to obtain 0.17 g of methyl 6-(2H-3,4-dihydrobenzo-1,4-oxazin-7-yl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinate having a melting point of 194 - 197°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1725, 1695.

Example 27

In 10 ml of methanol was dissolved 0.5 g of 6-(4-hydroxy-3-nitrophenyl)-4-oxo-1-(4-fluorophenyl)-1,4-dihydronicotinic acid, and to this solution was added 0.1 g of 5% by weight palladium carbon. The said acid was hydrogenated under atmospheric pressure for 2 hours. After completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to obtain 0.45 g of 6-(4-hydroxy-3-aminophenyl)-4-oxo-1-(4-fluorophenyl)-1,4-dihydronicotinic acid having a melting point of 231 - 233°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1730.

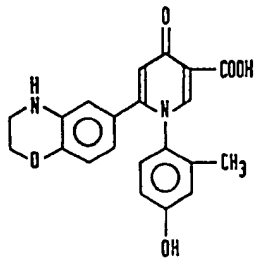
Example 28

In 7 ml of benzene was dissolved 0.6 g of methyl 5-(4-benzoyl-2H-3,4-dihydrobenzo-1,4-oxazin-6-yl)-3-oxo-4-pentenoate, and 0.2 g of N,N-dimethylformamidodimethylacetal was added to the solution. They were reacted at 60 - 70°C for 2 hours. The reaction mixture was cooled to room temperature, and 0.19 g of p-fluoroaniline was added thereto. The resulting mixture was subjected to reaction at room temperature for 4 hours. After completion of this reaction, the solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: toluene/ethyl acetate (20:1 by volume) mixture). The fraction containing the objective substance was concentrated and the crystals thus formed were dissolved in 5 ml of N,N-dimethylformamide, and they were refluxed for 5 hours. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform). The fraction containing the objective substance was concentrated, and the oily substance thus formed was dissolved in 5 ml of dioxane, and 0.11 g of 2,3,5,6,-tetrachloro-p-benzoquinone was added to the resulting solution. The solution was subjected to reaction at 80 - 90°C for 30 minutes. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and the residue was dissolved in 2 ml of chloroform. The insolubles were removed by filtration, and the filtrate was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform). The fraction containing the objective substance was concentrated, and to crystals thus formed were added 5 ml of ethanol and 5 ml of a 1 N aqueous sodium hydroxide solution, and they were reacted at room temperature for 2 hours. After completion of this reaction, ethanol was

removed by distillation under reduced pressure, and the residue was adjusted to a pH of 6.5 with acetic acid. The precipitated crystals were collected by filtration, washed with water, and dried to obtain 0.4 g of 6-(2H-3,4-dihydrobenzo-1,4-oxazin-6-yl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 155 - 167°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720.

The following compound was obtained in the same manner.



Melting point (°C): 205 - 207
IR (KBr) cm^{-1}: $\nu_{C=O}$ 1725.

Example 29

In 5 ml of benzene was dissolved 0.3 g of methyl 5-phenyl-3-oxo-4-pentenate, and 0.2 g of N,N-dimethylformamidodimethylacetal was added to the solution. They were reacted at 60 - 70°C for 2 hours. The reaction mixture was cooled to room temperature, and 0.3 g of 4-(4-acetylpiperazino)-aniline was added thereto. The mixture was subjected to reaction at room temperature for 4 hours. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and the oily substance thus obtained was dissolved in 5 ml of N,N-dimethylformamide, and they were refluxed for 5 hours. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform/ethanol (25:1 by volume) mixture). The fraction contalning the objective substance was concentrated, and the oily substance thus obtained was dissolved in 4 ml of dioxane, and 0.12 g of 2,3,5,6-tetrachloro-p-benzoquinone was added thereto. They were reacted at 90 - 100°C for 30 minutes. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform/ethanol (100:3 by volume) mixture). The fraction containing the objective substance was concentrated, and to the crystals thus formed were added 3 ml of 6 N hydrochloric acid, and the resulting mixture was refluxed for 2 hours. Water was removed by distillation under reduced pressure, to obtain 0.12 g of 6-phenyl-1-(4-piperazinophenyl)-4-oxo-1,4-dihydronicotinic acid dihydrochloride having a melting point of 211 - 213°C (decomp.)

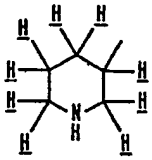
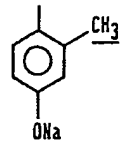
IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720, 1695.

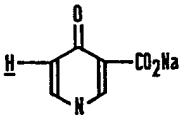
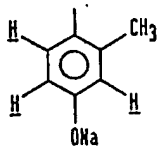
Example 30

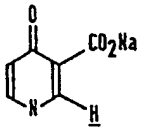
5 ml of methanol was carefully added to 0.05 g of 5% by weight palladium carbon under ice cooling, and this mixture was stirred under a hydrogen atmosphere for 20 minutes, followed by addition of a solution of 0.4 g of methyl 6-(1-benzyloxycarbonyl-3-piperidinyl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinate in 2 ml of methanol, and the mixture was subjected to hydrogenation under atomspheric pressure for 4 hours. After complection of the reaction, the palladium carbon was removed by filtration, and the solvent was removed by distillation under reduced pressure. The residue was dissolved in 5 ml of methanol, and 1.4 ml of 1 N aqueous sodium hydroxide was added thereto, and they were reacted at room temperature for 10 minutes. Thereafter, the solvent was removed by distillation under reduced pressure, to obtain 0.15 g of disodium 6-(3-piperidinyl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinate having a melting point of 250°C or more.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1630.

NMR (d_6-DMSO-D_2O) δ values:

0.88-3.17 (12H, m,  , ),

6.50-7.21 (4H, m,  , ),

8.07 (1H, s, ).

Example 31

(1) 5 ml of methanol was carefully added to 0.06 g of 5% by weight palladium carbon under ice cooling, and this mixture was stirred under a hydrogen atomosphere at room temperature for 20 minutes, followed by addition of a solution of 0.4 g of methyl 6-(1-benzyloxycarbonyl-4-piperidinyl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinate in 2 ml of methanol, and the mixture was subjected to hydrogenation under atomospheric pressure for 4 hours. After completion of the reaction, the palladium carbon was removed by filtration and the solvent was removed by distillation under reduced pressure to obtain 0.24 g of methyl 6-(4-piperidinyl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinate having a melting point of 226 - 228°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1730.

(2) In 4 ml of N,N-dimethylformamide was dissolved 0.24 g of methyl 6-(4-piperidinyl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinate, and 0.17 g of isopropyl bromide and 0.06 g of potassium carbonate were added to the solution, after which they were reacted at 60°C for 6 hours. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and the residue was dissolved in a mixture of 20 ml of chloroform and 20 ml of water. The organic layer was separated, washed twice with 20-ml portions of water, and dried with anhydrous sodium sulfate. Then, the solvent was removed by distillation under reduced pressure, and the oily substance thus obtained was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform/ethanol (20:1 by volume) mixture). The fraction containing the objective substance was concentrated, and to the oily substance thus obtained was added 5 ml of 6 N hydrochloric acid, and they were refluxed for 2 hours. The solvent was removed by distillation under reduced pressure to obtain 0.11 g of 1-(4-hydroxy-2-methylphenyl)-6-(1-isopropyl-4-piperdidinyl)-4-oxo-1,4-dihydronicotinic acid hydrochloride having a melting point of 195.5 - 200.5°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720.

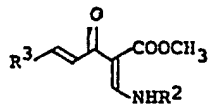
Example 32

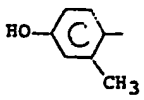
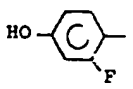
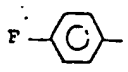
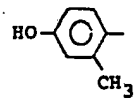
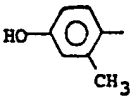
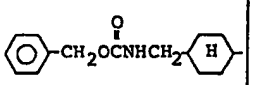
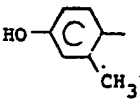
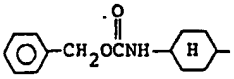
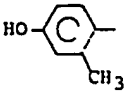
(1) In 20 ml of benzene was dissolved 2.0 g of methyl 5-(cyclohezen-4-yl)-3-oxo-4-pentenoate, and 1.4 g of N,N-dimethylformamidodimethylacetal was added thereto. They were reacted at 70°C for 1.5 hours. This reaction mixture was cooled to room temperature, and 1.2 g of p-hydroxyaniline was added thereto. They were reacted for 1.5 hours. After completion of the reaction, 50 ml of diisopropyl ether was added to the reaction mixture and the precipitated crystals were collected by filtration and washed with 20 ml of diisopropyl ether to obtain 2.1 g of methyl 5-(cyclohexen-4-yl)-2-(4-hydroxyphenylaminomethylene)-3-oxo-4-pentenoate having a melting point of 151 - 153°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1710.

The compounds shown in Table 26 were obtained in the same manner.

TABLE 26



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		173 - 175	1705, 1655
		142 - 147	1700, 1660
		-	1700 (neat)
		167 - 169	1700, 1680, 1660
		167 - 168	1720, 1700
		141 - 145	1725, 1695
		120 - 130	1725, 1710

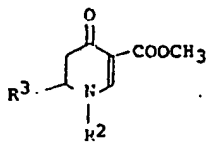
(2) In 20 ml of N,N-dimethylformamide was dissolved 2.0 g of methyl 5-(cyclohexen-4-yl)-2-(4-hydroxyphenylaminomethylene)-3-oxo-4-pentenoate, and they were reacted at 140°C for 4 hours. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and to the residue was added 50 ml of dioxane, after which the precipitated crystals were collected by filtration and washed with 30

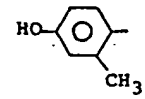
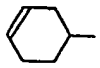
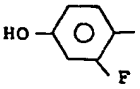
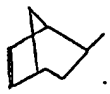
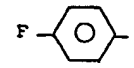
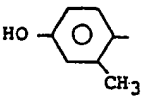
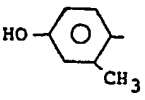
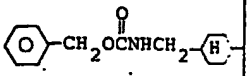
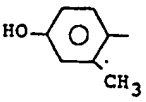
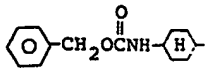
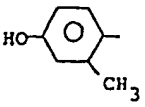
ml of diethyl ether to obtain 1.4 g of methyl 6-(cyclohexen-4-yl)-1-(4-hydroxyphenyl)-4-oxo-1,4,5,6-tetrahydronicotinate having a melting point of 155 - 157°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1715.

The compounds shown in Table 27 were obtained in the same manner.

TABLE 27

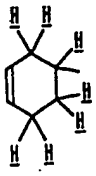


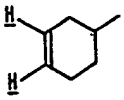
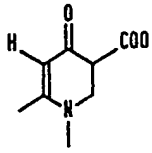
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		217 - 219	1720, 1690
		154 - 157	1720, 1705
		-	1720 (neat)
		201 - 205	1720, 1710
		197 - 201	1725, 1710, 1670
		105 - 110	1725, 1710
		110 - 120	1720

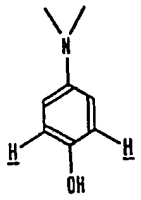
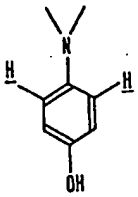
(3) In 20 ml of dioxane was dissolved 1.0 g of methyl 6-(cyclohexen-4-yl)-1-(4-hydroxyphenyl)-4-oxo-1,4,5,6-tetrahydronicotinate, and the resulting solution was heated to 80°C. To this solution was added dropwise a solution of 0.83 g of 2,3,5,6-tetrachloro-p-benzoquinone in 20 ml of dioxane at 80°C, followed by reaction at the same temperature for 1 hour. After completion of this reaction, the reaction mixture was

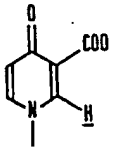
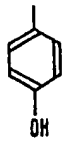
cooled to room temperature, and the precipitated crystals were collected by filtration and washed with 50 ml of dioxane to obtain 0.7 g of methyl 6-(cyclohexen-4-yl)-1-(4-hydroxyphenyl)-4-oxo-1,4-dihydronicotinate having a melting point of 250°C or more.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1735, 1705.
NMR (d_6-DMSO) δ values:

1.5-2.65 (7H, m, ), 3.73 (3H, s, $-COOCH_3$),

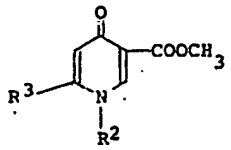
5.65 (2H, bs, ), 6.34 (1H, s, ),

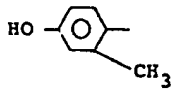
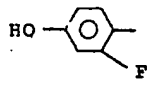
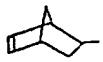
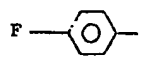
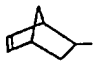
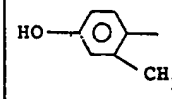
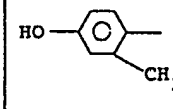
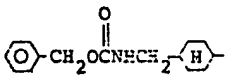
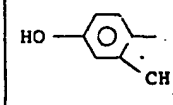
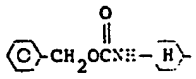
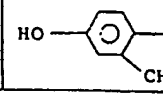
6.97 (2H, d, J=9Hz, ), 7.45 (2H, d, J=9Hz, ),

8.12 (1H, s, ), 10.12 (1H, s, )

The compounds shown in Table 28 were obtained in the same manner.

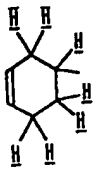
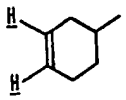
TABLE 28

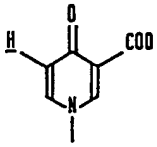
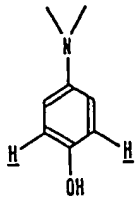


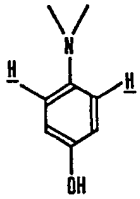
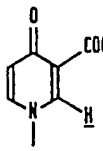
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>250	1730
		>250	1735, 1705
		247 - 249	1725
		240 - 243	1730, 1700
		254 - 257	1725, 1695
		130 - 135	1725, 1710
		150 - 158	1720, 1700

(4) In a mixture consisting of 5 ml of methanol and 5 ml of a 1 N aqueous sodium hydroxide solution was dissolved 0.5 g of methyl 6-(cyclohexen-4-yl)-1-(4-hydroxyphenyl)-4-oxo-1,4-dihydronicotinate, and they were reacted at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was adjusted to a pH of 5.5 with acetic acid, and the precipitated crystals were collected by filtration, washed with 30 ml of water, and dried to obtain 0.35 g of 6-(cyclohexen-4-yl)-1-(4-hydroxyphenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 250°C or more.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1725, 1700.
NMR (d_6-DMSO) δ values:

1.5-2.5 (7H, m, ), 5.50 (2H, s, ),

6.77 (1H, s, ), 6.88 (2H, d, J=9Hz, ),

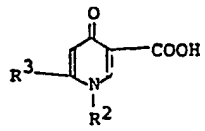
7.40 (2h, d, J=9Hz, ), 8.28 (1H, s, ),

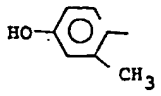
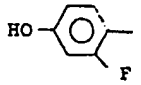
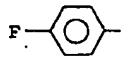
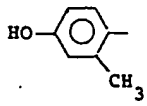
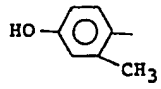
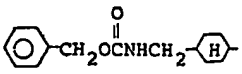
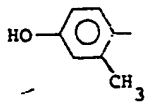
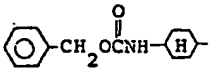
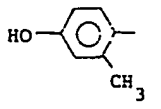
10.05 (1H, bs, )

7.40 (2H, d, J=9Hz,

The compounds shown in Table 29 were obtained in the same manner.

TABLE 29



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>250	1725, 1710
		242 - 243	1742
		195 - 197	1715
		150 - 165	1720
		259 - 261	1725, 1710
		271 - 273	1730, 1685
		190 - 200	1720, 1705, 1690

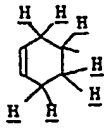
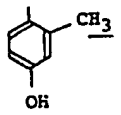
Example 33

In 30 ml of N,N-dimethylformamide was dissolved 2.0 g of methyl 5-(cyclohexen-4-yl)-3-oxo-4-pentenoate and 1.4 g of N,N-dimethylformamidodimethylacetal was added thereto. They were reacted at 70°C for 1.5 hours. To the reaction mixture was then added 1.3 g of 4-hydroxy-2-methylaniline at 70°C, and the resulting mixture was subjected to reaction at 80°C for 2 hours and at 140°C for 3 hours. After completion of this reaction, the reaction mixture was cooled to room temperature, and the solvent was removed by distillation in 20 ml of dioxane, and a solution of 2.4 g of 2,3,5,6-tetrachloro-p-benzoquinone in 15 ml of dioxane was added dropwise thereto at 80°C, followed by reaction at the same temperature for one hour. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and the residue was suspended in 30 ml of chloroform and 30 ml of water. After adhusting the pH of the suspension to 7.5 with sodium hydrogencarbonate, the organic layer was separated, washed successively with 10 ml of water

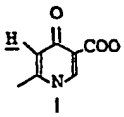
and 20 ml of a saturated aqueous solution of sodium chloride, and then dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain 1.3 g of methyl 6-(cyclohexen-4-yl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinate having a melting point of 250°C or more.

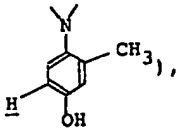
IR (KBr) cm^{-1}: $\nu_{C=O}$ 1735, 1705.

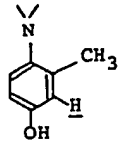
NMR (d_6-DMSO) δ values:

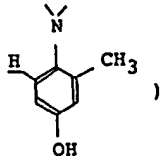
1.5-2.5 (10H, m,  , ),

3.82 (3H, s, -COOCH$_3$), 5.67 (2H, s, ),

6.46 (1H, s, ),

6.88 (1H, d, J=9Hz, ),

6.97 (1H, s, ),

7.47 (1H, d, J=9Hz, ),

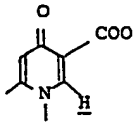
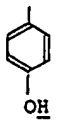
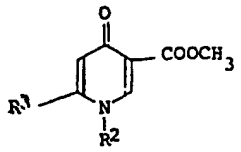
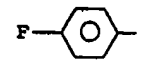
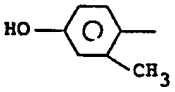
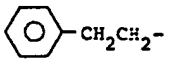
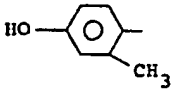
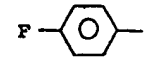
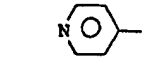
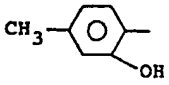
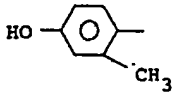
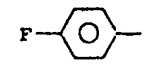
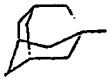
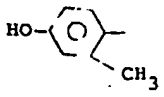
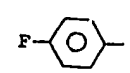
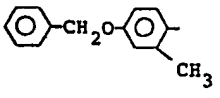
8.14 (1H, s, ), 10.0 (1H, s, )

TABLE 30



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		252 - 254	1730
		>250	1725, 1705
		>250	1725, 1700
		>250	1725
		>250	1730
		>250	1735, 1705
$CH_3CH{=}CH-$ (trans)		162 - 164	1740
		286 - 288	1740
		293 - 294	1730-1710
		204 - 205	1730
$ClCH_2CH_2-$		118 - 120	1730

Example 34

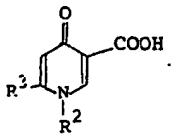
In 80 ml of chloroform was dissolved 2.0 g of methyl 6-(cyclohexen-4-yl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinate and the solution was cooled to 5°C. To this solution was added dropwise a solution of 1.0 g of bromine in 5 ml of chloroform at 5°C over 30 minutes. The mixture was subjected to reaction at room temperature for 30 minutes. After completion of the reaction, the solvent was removed by distillation under reduced pressure. Then, 50 ml of diethyl ether was added to the resulting residue, and the precipitated crystals were collected by filtration and washed with 20 ml of diethyl ether to obtain 2.5 g of methyl 6-(3,4-dibromocyclohexyl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinate having a melting point of 197 - 200°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1730, 1700

Example 35

The compounds shown in Table 31 were obtained by hydrolyzing the corresponding methyl esters in the same manner as in Example 32-(4).

TABLE 31



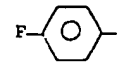
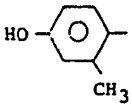
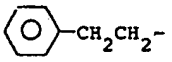
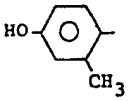
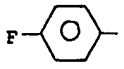
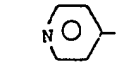
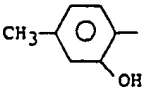
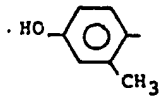
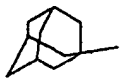
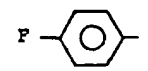
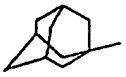
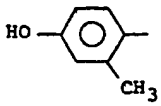
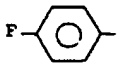
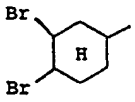
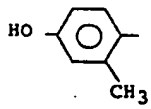
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		235 - 236	1715
		175 - 178	1725, 1705
		226 - 227	1725
		182 - 184	1720
		171 - 174	1720
		>250	1720, 1710

TABLE 31 (cont'd)

$CH_3CH=CH-$ (trans)		245 - 248	1730
		>280	1720
		>280	1730, 1710, 1690, 1660
		172 - 173	1725
		183 - 185	1725

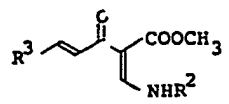
Example 36

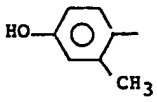
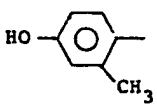
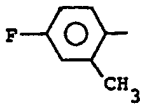
(1) In 5 ml of benzene was dissolved 0.7 g of methyl 5-(cyclopenten-1-yl)-3-oxo-4-pentenoate, and 0.6 g of N,N-dimethylformamidodimethylacetal was added thereto. They were reacted at 70°C for 1.5 hours. The reaction mixture was cooled to room temperature, and 0.44 g of 4-hydroxy-2-methylaniline was added thereto. The resulting mixture was subjected to reaction for addtional 1.5 hours. After completion of the reaction, 5 ml of diethyl ether was added, and the precipitated crystals were collected by filtration, and washed with 5 ml of diethyl ether to obtain 0.7 g of methyl 5-(cyclopenten-1-yl)-2-(4-hydroxy-2-methylphenylaminomethylene)-3-oxo-4-pentenoate having a melting point of 148 - 151°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1705.

The compounds shown in Table 32 were obtained in the same manner.

TABLE 32



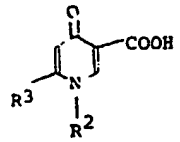
R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		161 - 162	1700
		145 - 148	1660
		168 - 170	1700

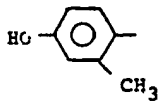
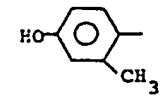
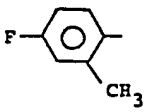
(2) In 5 ml of N,N-dimethylformamide was dissolved 0.7 g of methyl 5-(cyclopenten-1-yl)-2-(4-hydroxy-2-methylphenylaminomethylene)-3-oxo-4-pentenoate, and they were reacted at 140°C for 2 hours. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform) to obtain an oily substance. This oily substance was dissolved in 10 ml of dioxane, and 0.5 g of 2,3,5,6-tetrachloro-p-benzoquinone was added thereto. They were reacted at 80°C for 30 minutes. The reaction mixture was cooled to room temperature, and the precipitated crystals were collected by filtration, and washed with 5 ml of dioxane. These crystals were dissolved in a mixture of 5 ml of methanol and 5 ml of a 1 N aqueous sodium hydroxide solution, the resulting mixture was subjected to reaction at room temperature for 30 minutes. The reaction mixture was adjusted to a pH of 5.5 with acetic acid and the precipitated crystals were collected by filtration, washed with water, and dried to obtain 0.3 g of 6-(cyclopenten-1-yl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 211 - 213°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720, 1700.

The compounds shown in Table 33 were obtained in the same manner.

TABLE 33



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>250	1720, 1710
		>250	1730, 1725
		162 - 164	1720

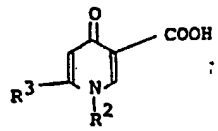
Example 37

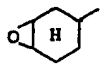
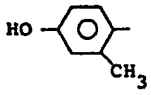
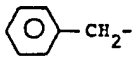
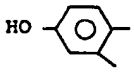
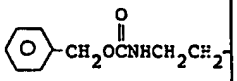
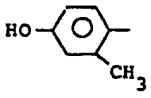
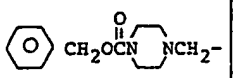
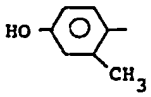
In 5 ml of benzene was dissolved 0.3 g of methyl 5-cyclooctyl-3-oxo-4-pentenoate, and 0.3 g of N,N-dimethylformamidodimethylacetal was added thereto. They were reacted at 70°C for one hour. Then, the reaction mixture was cooled to room temperature, and 0.27 g of 4-hydroxy-2-methylaniline was added thereto. The resulting mixture was subjected to reaction at room temperature for 2 hours. After completion of this reaction, the solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: toluene/ethyl acetate (50:1 by volume) mixture). The fraction containing the objective substance was concentrated, and the oily substance thus obtained was dissolved in 5 ml of N,N-dimethylformamide and the resulting mixture was refluxed for 4 hours. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform/ethanol (50:1 by volume) mixture). The fraction containing the objective substance was concentrated and the oily substance thus obtained was dissolved in 5 ml of dioxane, and 0.2 g of 2,3,5,6-tetrachloro-p-benzoquinone was added thereto, and they were reacted at 80 - 90°C for 30 minutes. The reaction mixture was cooled to room temperature, and the precipitated crystals were collected by filtration. These crystals were dissolved in 20 ml of chloroform, and after removing the insolubles, the chloroform was removed by distillation under reduced pressure. To the residue were added 5 ml of a 1 N aqueous sodium hydroxide solution and 5 ml of methanol, and they were reacted at room temperature for 30 minutes. After the methanol was removed by distillation under reduced pressure, the resulting solution was adjusted to a pH of 6.5 with 2 N hydrochloric acid, and the precipitated crystals were collected by filtration, washed with water, and dried to obtain 0.14 g of 6-cyclooctyl-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 118 - 120°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1725, 1710.

The compounds shown in Table 34 were obtained in the same manner.

TABLE 34



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		>270	1720
		229 - 232	1720
		102 - 104	1720
		115 - 118	1720, 1700

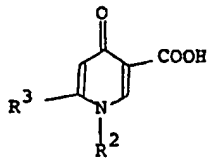
Example 38

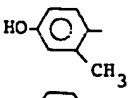
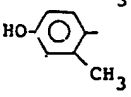
In a mixture of 10 ml of dioxane and 5 ml of water was dissolved 0.15 g of 6-(4-benzyloxycarbonyl-aminocyclohexyl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinic acid, and 0.03 g of 5% by weight palladium carbon was added. The above acid was hydrogenated under atmospheric pressure for 3 hours. The catalyst was removed by filtration and the solvent was then removed by distillation under reduced pressure. To the residue was added 3 ml of diethyl ether, and the precipitated crystals were collected by filtration and washed with 3 ml of diethyl ether to obtain 0.095 g of 6-(4-aminocyclohexyl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 237 - 250°C (decomp.).

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1715.

The compounds shown in Table 35 were obtained in the same manner.

TABLE 35



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
$Et_2NCH_2CH_2-$		220-225	1725, 1710, 1690
		>250	1720

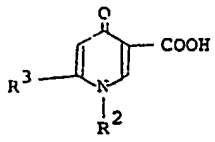
Example 39

In 15 ml of methanol was dissolved 0.2 g of methyl 6-(4-benzyloxycarbonylaminocyclohexyl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinate, and 0.05 g of 5% by weight palladium carbon was added to the resulting solution, and the above ester was hydrogenated under atmospheric pressure for 1.5 hours. Then, the catalyst was removed by filtration, and the solvent was removed by distillation under reduced pressure. To the residue were added 0.4 g of 37% by weight formalin and 0.1 g of formic acid, and they were reacted at 100°C for 7.5 hours. After completion of this reaction, the solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform/ethanol (3:1 by volume) mixture) to obtain 0.04 g of 6-(4-dimethylamino-cyclohexyl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 207 - 215°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720.

The compound shown in Table 36 was obtained in the same manner.

TABLE 36



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
$(CH_3)_2NCH_2$- 		177-183	1720

Example 40

(1) In 315 ml of dioxane was dissolved 10.5 g of methyl 1-(4-acetoxy-2-methylphenyl)-6-methyl-4-oxo-1,4-dihydronicotinate under heating, and 4.43 g of selenium dioxide was added thereto. They were reacted at 100°C for 2 hours. After cooling the reaction mixture, to room temperature, selenium was removed by filtration, and then the solvent was removed by distillation under reduced pressure. The residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform/ethanol (25:1 by volume) mixture) to obtain 7.9 g of methyl 1-(4-acetoxy-2-methylphenyl)-6-formyl-4-oxo-1,4-dihydronicotinate having a melting point of 216 - 217°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1760, 1730, 1700 (sh)

(2) To 0.95 g of methyl 1-(4-acetoxy-2-methylphenyl)-6-formyl-4-oxo-1,4-dihydronicotinate was added 5 ml of 6 N hydrochloric acid, and they were reacted at 100°C for one hour. The reaction mixture was cooled to room temperature, and adjusted to a pH of 7.5 with a saturated aqueous sodium hydrogencarbonate solution. Then, 100 ml of acetonitrile was added, and the aqueous layer was saturated with sodium chloride. The organic layer was separated, washed with a saturated aqueous solution of sodium chloride and then dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain 0.6 g of 6-formyl-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 230 - 250°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1715.

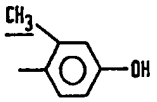
(3) In 5 ml of methanol was dissolved 0.15 g of 6-formyl-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinic acid, and 0.19 g of ethoxycarbonylmethylenetriphenylphospholane was added thereto. They were reacted at room temperature for one hour. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform/ethanol (50:1 by volume) mixture) to obtain 0.06 g of 6-(2-ethoxycarbonylethenyl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 185 - 189°C.

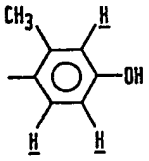
IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720, 1705.

(4) To 0.09 g of 6-(2-ethoxycarbonylethenyl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinic acid was added 3 ml of 6 N hydrochloric acid, and they were reacted at 100°C for 1.5 hours. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and to the crystals thus formed were added 3 ml of diethyl ether, and the resulting mixture was filtered to obtain 0.08 g of 6-(2-carboxy-ethenyl)-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 280°C or more.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720.

NMR (d_6-DMSO) δ values:

2.0 (3H, s, ),

6.33-7.7 (6H, m,  , C_5–H, –C*H*=C*H*–),

8.63 (1H, s, C_2–H)

Example 41

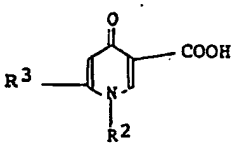
In 5 ml of methanol was dissolved 0.15 g of 6-formyl-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinic acid, and 0.056 g of N-aminomorpholine was added thereto. They were reacted at 65°C for one hour. After completion of this reaction, the solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform) to

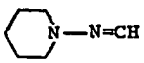
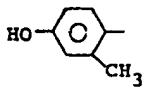
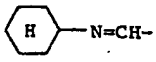
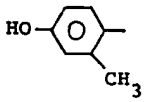
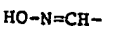
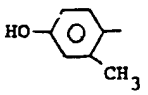
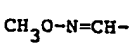
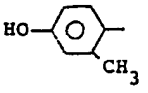
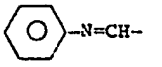
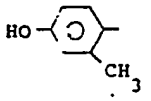
obtain 0.06 g of 1-(4-hydroxy-2-methylphenyl)-6-(morpholinoiminomethyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 267 - 268°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1730.

The compounds shown in Table 37 were obtained in the same manner.

TABLE 37



R^3	R^2	m.p. (°C)	IR (KBr) cm^{-1}: $\nu_{C=O}$
		249 - 250	1725
		193 - 199	1725, 1710 1695
		268 - 269	1715
		269 - 271	1730, 1710
		264 - 266	1750

Example 42

In 20 ml of N,N-dimethylformamide was dissolved 2 g of methyl 1-(4-benzyloxy-2-methylphenyl)-6-(2-chloroethyl)-4-oxo-1,4-dihydronicotinate, and 0.9 g of 4-ethyl-2,3-dioxopiperazine-1-sodium was added thereto at 5°C over 20 minutes, and they were reacted at the same temperature for 30 minutes. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of chloroform, washed successively with 20 ml of water and 20 ml of a saturated aqueous solution of sodium chloride and then dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to obtain an oily substance, and this oily substance was dissolved in a mixture of 10 ml of methanol and 10 ml of a 1 N aqueous sodium hydroxide solution. They were reacted at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was adjusted to a pH of 6.0 with acetic acid, and the precipitated crystals were collected by filtration, washed with water, and then dissolved in 10 ml of dioxane and 5 ml of water. Further, 0.2 g of 5% by weight palladium carbon was added thereto, and the resulting mixture was subjected to hydrogenation for 10 hours. After completion of this reaction, the reaction mixture was filtered, and the filtrate was concentrated under

reduced pressure to obtain 0.8 g of 6-[2-(4-ethyl-2,3-dioxopiperazin-1-yl)-ethyl]-1-(4-hydroxy-2-methylphenyl)-4-oxo-1,4-dihydronicotinic acid having a melting point of 182 - 190°C (decomp.).

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1730.

Example 43

In 20 ml of benzene was dissolved 3.0 g of methyl 7-(4-benzyloxycarbonyl-piperazin-1-yl)-3-oxo-4-heptenoate, and 1.2 g of N,N-dimethylformamidodimethylacetal was added thereto. They were reacted at 70°C for 1.5 hours. The reaction mixture was cooled to room temperature, and 1.0 g of 4-hydroxy-2-methylaniline was added thereto. The resulting mixture was subjected to reaction at the same temperature for 1.5 hours. After completion of this reaction, the precipitated crystals were collected by filtration, and washed with 10 ml of benzene. The crystals thus formed were dissolved in 20 ml of N,N-dimethylformamide, and they were reacted at 140°C for 3 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, and the solvent was removed by distillation under reduced pressure. The residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform) to obtain an oily substance. This oily substance was dissolved in 20 ml of dioxane, and 0.7 g of 2,3,5,6-tetrachloro-p-benzoquinone was added thereto, and they were reacted at 80°C for 30 minutes. After completion of the reaction, the reaction mixture was cooled to room temperature, and the precipitated crystals were collected by filtration, and washed with 10 ml of dioxane. The resulting crystals were dissolved in 10 ml of a 1 N aqueous sodium hydroxide solution, and the resulting solution was subjected to reaction at room temperature for 30 minutes. The reaction mixture was adjusted to a pH of 6.0 with acetic acid, and the precipitated crystals were collected by filtration, washed with water, and then dissolved in 10 ml of dioxane and 5 ml of water. Further, 0.2 g of 5% by weight palladium carbon was added thereto. The resulting mixture was subjected to hydrogenation under atmospheric pressure for 2 hours. After completion of the reaction, to the reaction mixture was added 5 ml of 2 N hydrochloric acid, and the resulting mixture was filtered, after which the filtrate was concentrated to obtain 0.4 g of 1-(4-hydroxy-2-methylphenyl)-6-[2-(piperazine-1-yl)-ethyl]-4-oxo-1,4-dihydronicotinic acid dihydrochloride having a melting point of 140 - 148°C.

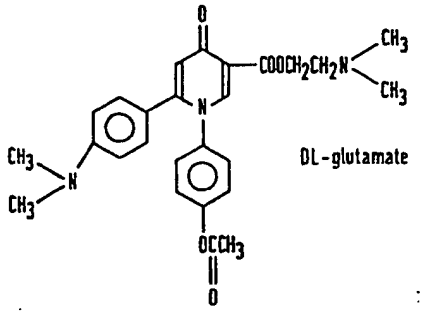
IR (KBr) cm^{-1}: $\nu_{C=O}$ 1720

Example 44

In 5 ml of water was suspended 0.15 g of dimethylaminoethyl 1-(4-acetyloxyphenyl)-6-(4-dimethylaminophenyl)-4-oxo-1,4-dihydronicotinate at room temperature, and 0.04 g of L-aspartic acid was added thereto. They were reacted at 60°C for 30 minutes, and the reaction mixture was cooled to room temperature. The insolubles were removed by filtration, and the solvent was removed by distillation under reduced pressure. The residue was dehydrated azeotropically with toluene and dried to obtain 1.2 g of L-aspartate salt of dimethylaminoethyl 1-(4-acetyloxyphenyl)-6-(4-dimethylaminophenyl)-4-oxo-1,4-dihydronicotinate having a melting point of 144 - 147°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1760, 1725, 1700

The following compound was obtained in the same manner:



Melting point (°C): 115 - 118.
IR (KBr) cm^{-1}: $\nu_{C=O}$ 1760, 1725, 1700.

Example 45

In 20 ml of methylene chloride was dissolved 0.8 g of 1-(4-acetyloxyphenyl)-6-(4-dimethylaminophenyl)-4-oxo-1,4-dihydronicotinic acid, and the resulting solution was cooled to 5°C. To this solution was added dropwise 0.3 g of oxalyl chloride at the same temperature, and they were reacted for one hour. After completion of the reaction, 0.84 g of 1,2-O-isopropylidene glycerin and 0.26 g of triethylamine were added successively at the same temperature, and the resulting mixture was further subjected to reaction for 2

hours. This reaction mixture was introduced into 50 ml of ice water, and the organic layer was separated, washed successively with 50 ml of water and then with 50 ml of a saturated aqueous solution of sodium chloride, and dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure, and the residue was suspended in 15 ml of 60% by weight acetic acid. The suspension was subjected to reaction at 60°C for 3 hours. After completion of this reaction, the solvent was removed by distillation under reduced pressure, and the residue was purified by a column chromatography (Wako Silica Gel C-200; eluent: chloroform/ethanol (15:1 by volume) mixture) to obtain 0.3 g of 2,3-dihydroxypropyl 1-(4-acetyloxyphenyl)-6-(dimethylaminophenyl)-4-oxo-1,4-dihydronicotinate having a melting point of 145 - 147°C.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1760, 1730, 1680.

Preparation Example 1

With 50 g of 1-pivaloyloxyethyl 6-(4-dimethylaminophenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinate were mixed 49 g of crystalline cellulose, 50 g of corn starch and 1 g of magnesium stearate, and the resulting mixture was tableted into 1,000 flat tablets.

Preparation Example 2

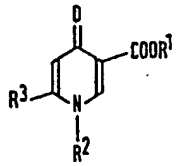
With 100 g of 1-pivaloyloxyethyl 6-(4-dimethylaminophenyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydronicotinate was mixed 50 g of corn starch, and the resulting mixture was encapsulated to form 1,000 capsules.

Preparation Example 3

In a suitable amount of distilled water for injection were dissolved 200 mg of sodium 1-(2-fluoro-4-hydroxyphenyl)-6-(1-methylindol-5-yl)-4-oxo-1,4-dihydronicotinate and 250 mg of dextrose, and this solution was placed in a 5-ml ampule. After purging with nitrogen, the ampul was sterilized under pressure at 121°C for 15 minutes to obtain an injection.

CLAIMS

1. A 4-oxo-1,4-dihydronicotinic acid derivative or its salt, said derivative being represented by the formula:



wherein R^1 represents a hydrogen atom or a carboxyl-protecting group, R^2 represents a substituted aryl group or a substituted or unsubstituted heterocyclic group; and R^3 represents a haloalkyl group, an aminoalkyl group or a substituted or unsubstituted alkenyl, aralkenyl, aralkyl, aralkadienyl, aralkynyl, heterocyclic alkyl, heterocyclic alkenyl, aryl, cycloalkyl, cycloalkenyl, acyl, iminoalkyl, heterocyclic or bridged hydrocarbon group.

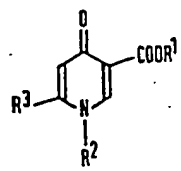
2. A 4-oxo-1,4-dihydronicotinic acid derivative or its salt according to Claim 1, wherein R^3 represents a substituted or unsubstituted aralkenyl, aralkadienyl, aralkynyl, aryl, heterocyclic alkenyl or heterocyclic group.

3. A 4-oxo-1,4-dihydronicotinic acid derivative or its salt according to Claim 1, wherein R^3 is a haloalkyl group, an aminoalkyl group, or a substituted or unsubstituted alkenyl, cycloalkyl, cycloalkenyl, aralkyl, heterocyclic alkyl, iminoalkyl, acyl or bridged hydrocarbon group, provided that the case where the alkenyl group is substituted by an aryl or heterocyclic group is excluded.

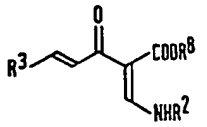
4. A 4-oxo-1,4-dihydronicotinic acid derivative or its salt according to Claim 1, 2 or 3, wherein R^2 represents a substituted aryl group.

5. A 4-oxo-1,4-dihydronicotinic acid derivative or its salt according to Claim 4, wherein the substituted aryl group is a phenyl or naphthyl group substituted by at least one substituent selected from the group consisting of a halogen atom and hydroxyl and alkyl groups.

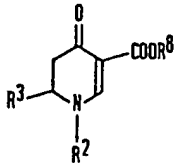
6. A process for producing a 4-oxo-1,4-dihydronicotinic acid derivative or its salt, said derivative being represented by the formula:



wherein R^1 represents a hydrogen atom or a carboxyl-protecting group; R^2 represents a substituted aryl group or a substituted or unsubstituted heterocyclic group; and R^3 represents a haloalkyl group, an aminoalkyl group or a substituted or unsubstituted alkenyl, aralkenyl, aralkyl, aralkadienyl, aralkynyl, heterocyclic alkyl, heterocyclic alkenyl, aryl, cycloalkyl, cycloalkenyl, acyl iminoalkyl, heterocyclic or bridged hydrocarbon group, which comprises subjecting to ring-closure reaction a compound represented by the formula:

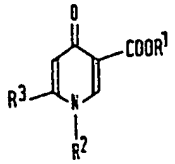


wherein R^2 and R^3 have the same meanings as defined above, and R^8 represents the same carboxyl-protecting group as R^1, to obtain a 4-oxo-1,4,5,6-tetrahydronicotinic acid derivative represented by the formula:

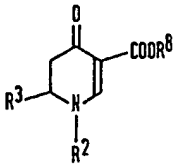


wherein R^2, R^3 and R^8 have the same meanings as defined above, and then subjecting the thus obtained derivative to dehydrogenation reaction, and if desired, to removal of the carboxyl-protecting group.

7. A process for producing a 4-oxo-1,4-dihydronicotinic acid derivative or its salt, said derivative being represented by the formula:

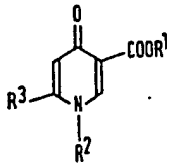


wherein R^1 represents a hydrogen atom or a carboxyl-protecting group; R^2 represents a substituted aryl group or a substituted or unsubstituted heterocyclic group; and R^3 represents a haloalkyl group, an aminoalkyl group or a substituted or unsubstituted alkenyl, aralkenyl, aralkyl, aralkadienyl, aralkynyl, heterocyclic alkyl, heterocyclic alkenyl, aryl, cycloalkyl, cycloalkenyl, acyl, iminoalkyl, heterocyclic or bridged hydrocarbon group, which comprises subjecting to dehydrogenation a 4-oxo-1,4,5,6-tetrahydronicotinic acid derivative represented by the formula:



wherein R^2 and R^3 have the same meanings as defined above and R^8 represents the same carboxyl-protecting group as R^1, and if desired, to removal of carboxyl-protecting group.

8. An antibacterial agent comprising a 4-oxo-1,4-dihydronicotinic acid derivative or its salt, said derivative being represented by the formula:



wherein R^1 represents a hydrogen atom or a carboxyl-protecting group; R^2 represents a substituted aryl group or a substituted or unsubstituted heterocyclic group; and R^3 represents a haloalkyl group, an aminoalkyl group or a substituted or unsubstituted alkenyl, aralkenyl, aralkyl, aralkadienyl, aralkynyl, heterocyclic alkyl, heterocyclic alkenyl, aryl, cycloalkyl, cycloalkenyl, acyl, iminoalkyl, heterocyclic or bridged hydrocarbon group.

9. A derivative as claimed in claim 1 and substantially as described in any one of the specific examples hereinbefore set forth.

10. A process as claimed in claim 9 and substantially as described in any one of the specific examples hereinbefore set forth.

11. Each and every novel embodiment herein set forth when considered either separately or in combination.

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